AIMED ALLIANCE
Alliance for the Adoption of Innovations in Medicine

August 30, 2017

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Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine ("Aimed Alliance") is a nonprofit organization that works to expand access to quality health care in the U.S. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the "Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions," ("Report") published by the Institute for Clinical and Economic Review ("ICER").

Rare diseases are those that affect fewer than 200,000 people in the U.S.[1] They can be chronic, debilitating, and sometimes deadly, and yet, there is often only one or no treatment available for such diseases, leaving patients with very few options for care. While there are 7,000 rare diseases in the U.S. that affect approximately 30 million individuals,[2] only 450 treatments approved by the U.S. Food and Drug Administration ("FDA") exist for these diseases.[3] Such treatments, referred to as orphan drugs, have helped the lives of hundreds of thousands of patients suffering from rare diseases.[4] We are concerned that the Report may limit access to those treatments.

A. Use of QALYs Is Inappropriate

Aimed Alliance recommends against relying on quality-adjusted life year ("QALY") measures to evaluate orphan treatments. The use of QALY measures to evaluate ultra-rare diseases raises significant ethical concerns. For example, individuals with rare diseases should have the same access to treatment as individuals with common diseases and conditions, regardless of whether the QALY gain is large. Yet, QALY measures put a price tag on the value of a human life that merely reflects the individual's diagnosis and deems those with chronic, debilitating, and rare conditions, as being worth less than those with common diseases. They treat individuals' lives and health as a commodity and ignore patients' and practitioners' individualized concept of the value of treatment.

QALYs are particularly inappropriate for rare and serious conditions because, as ICER stated in its previous report, it is not "cost effective" to prolong the life of someone with a serious condition.[5] Infants with rare diseases, such as spinal muscular atrophy, who are not expected to live more than a few years

[1] https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=126
[2] https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases
[3] http://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies
[4] http://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies
[5] https://icer-review.org/wp-content/uploads/2017/02/ICER_Assessing-the-Value-of-Drugs-for-Rare-Conditions_051017.pdf (stating "cost-effectiveness analysis uses patients' rating of quality of life in valuing the extension of life, which would mean that extension of life for patients with severe disability (and therefore worse quality of life) would result in higher (i.e., less favorable) cost-effectiveness ratios relative to patients with less disability, all else being equal.").

even with treatment, would have low QALYs, for example. Therefore, using this rationale, access to treatment would be significantly limited if a QALY calculation were used to determine whether individuals with rare and serious conditions should have access to treatment.

As ICER has acknowledged, many countries do not use QALYs for rare conditions, nor do they use cost-effectiveness in determining the value of orphan drugs.[6] Perhaps, then, it would be most appropriate to use outcomes-based assessments in which the price of the drug is refunded if it does not work for the patient.

Moreover, in the Report, ICER states that if it is not feasible to translate measures of patient outcomes into QALYs, it will provide analyses of the potential costs and consequences of treatment, and will not provide a value-based price benchmark. ICER will instead provide a cross walk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found. Aimed Alliance agrees that ICER should forego its QALY calculation in such a circumstance but cautions against comparing a treatment with the closest clinical analogue, especially given that many rare diseases only have one treatment, if any. There may be no appropriate clinical analogue, and an improper comparison can result in unnecessarily restricting access to the few treatment options that are available.

Finally, ICER acknowledges challenges that arise in generating evidence for treatments for rare conditions in the Report. In such cases, Aimed Alliance recommends refraining from assessing such treatments until accurate evidence is available to make a proper assessment.

B. The Scope Proposed for Assessing Ultra-Rare Orphan Drugs Is Overly Narrow and Arbitrary

Aimed Alliance appreciates that ICER is considering adapting its value assessment to take into account the unique circumstances of individuals with ultra-rare conditions. However, we are concerned that the criteria ICER plans to use to determine which conditions will be considered under the adapted framework are overly narrow and arbitrary. For example, the proposed value assessment would be limited to rare conditions that are determined to be both (1) ultra-rare and (2) serious.

Aimed Alliance recommends against limiting the scope of the proposed value assessment to "ultra-rare" conditions and instead consider broadening it to all rare conditions. While patients with common diseases typically have multiple treatments to choose from, including generics, treatment availability is often limited or may not exist at all for rare diseases in general. Currently, 95 percent of rare diseases do not have an FDA-approved treatment.[7] Therefore, when a treatment does become available, it is imperative that, when clinically indicated, patients with rare conditions have access to the treatment regardless of whether their condition is considered "rare" or "ultra-rare."

If the scope is to be limited to ultra-rare conditions, Aimed Alliances recommends using a different definition of "ultra-rare condition." As ICER acknowledges in the Report, there is currently no explicit definition of what constitutes an ultra-rare condition. Yet, ICER has proposed using a narrow, arbitrary set of factors for determining whether a condition will be considered under the adapted framework. A treatment will be considered under the adapted criteria if: (1) the treatment would be suitable for a patient population of fewer than 10,000; (2) there is little chance of future expansion of the indication or size of the treatment population to above 20,000 individuals; and (3) the treatment potentially offers a major gain in improved quality or length of life.

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[6] *Id.*

[77] http://healthaffairs.org/blog/2017/03/21/for-rare-disease-patients-a-pathway-to-hundreds-of-new-therapies/

Under the first factor, a patient population of 10,000 individuals is too restrictive. Although there is no definitive definition, ultra-rare diseases are generally defined as diseases or conditions that affect fewer than 20,000 individuals.[8] Furthermore, while the Report mentions patient population thresholds used by HTA in Italy and NICE in England, it is unclear exactly how ICER determined that a population size of 10,000 is an appropriate threshold.

Under the second factor, it is unclear how the chance of future expansion to a patient population of 20,000 will be determined. Proposing an arbitrary threshold can potentially prevent individuals with ultra-rare conditions from accessing treatments they need.

Under the third factor, ICER does not define what will constitute a "major" gain in the improved quality or length of life. For individuals with ultra-rare conditions, especially those with few treatment options, a modest, incremental gain may be meaningful and may significantly improve their quality or length of life. Therefore, Aimed Alliance recommends refraining from using such a small patient population, not limiting the patient population based on whether there is a chance of future expansion, and removing the criteria that the treatment offer a major gain in improved quality or length of life.

Additionally, ICER does not define "serious condition." Therefore, a determination that a condition is "serious" will be subjective in nature. While ICER may deem a condition "non-serious," those who have the condition or their health care providers may disagree. Moreover, regardless of whether a rare condition is considered serious or not, such individuals deserve effective treatment.

C. ICER Must Consider Patients' Perspective

Patients must have a meaningful role in the discussion of value. They are directly impacted by a report that seeks to define the effectiveness and value of their treatment options. Therefore, accounting for how patients define the value of their treatment options should be critical to ICER's analysis. While ICER states that it will consider input from patients and clinical experts on the potential impact of a new treatment and on "other benefits and disadvantages" and "contextual considerations" to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community, it is unclear how such factors will impact the benchmark calculation.

Conclusion

Thank you for the opportunity to comment on the Report. We are available for discussion to address our shared goals of access to high quality health care at a price that accurately reflects public and personal benefits in the final version of adapted methods.

Respectfully submitted,

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Executive Director

[8] http://www.centrichealthresources.com/documents/Centric_Pharmcom09.pdf; http://oplinc.com/newsletter/OplincSpecialReportAugust2015.html; http://pharmaceuticalcommerce.com/special-report/rare-diseases-and-orphan-drugs-lift-pharma-innovation/

Amgen Response to ICER's Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions

Executive Summary

Amgen appreciates the opportunity to comment on ICER's *"Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions"* and we hope that ICER will consider and incorporate our recommendations.

Amgen is concerned that ICER's proposed framework adaptation runs counter to the U.S. Orphan Drug Act (ODA) of 1983, the legislation designed to incentivize innovation and protect orphan disease patients. ICER has taken a positive step in its acknowledgement that orphan/ultra orphan diseases require special consideration. However, ICER's approach is contrary to both the ODA and the U.S. Federal Drug Administration (FDA) regulatory framework, which has special provisions for orphan diseases. This legislation provides incentives to address the significant societal burden and high-unmet need of the 25-30 million American patients with rare, disabling, burdensome, and almost uniformly fatal conditions.[1,2,3] Half of those with orphan diseases are children; an estimated 30 percent of children who have an orphan disease will not survive beyond their fifth birthday and only one in 10 orphan disease patients has a viable drug for their condition.[4]

ICER's proposed framework to assess the value of orphan drugs (through the common framework) and 'ultra-orphan' drugs (through the adapted framework) undervalues patients' suffering from often life-threatening orphan diseases and the medicines developed to treat them. Contrary to the Orphan Drug Act, ICER's proposed 'ultra-orphan' adapted framework ignores the majority of orphan diseases, subjecting them to ICER's common framework. The proposed adapted framework fails to capture the significant burden these conditions place on this population. It excludes the costs of patients, caregivers, employers and society, undervaluing the ability of new treatments to offset the significant burden of 'ultra-orphan' disease; it does the same to orphan diseases by defaulting to ICER's common framework. Moreover, in practice, no drug ICER has assessed to date, or plans to assess, would qualify as an ICER-defined 'ultra-orphan' drug.

ICER proposes a limit on how much should be spent on the health of orphan disease patients. ICER recommends a willingness-to-pay (WTP) threshold for orphan disease (by inappropriately applying the common disease framework) and for 'ultra-orphan' disease (through this adapted framework) in the U.S. This chosen WTP limit is not informed by what U.S. citizens or the government would want to spend. This will likely have consequences in slowing the pace of scientific innovation necessary to improve quality of life and potentially find cures for all ODA-defined diseases. Price thresholds similar to those seen in other countries is not only inappropriate for the U.S. system, but also well studied.[5,6] With 17 ODA-defined orphan drugs approved per year at the current pace, it would take nearly 400 years for researchers to find drugs for the millions of remaining patients.[7] This is in the absence of ICER's proposed approaches to the assessment of orphan and 'ultra-orphan' disease. However, the wide-reaching effects of this proposed value-framework for ODA-defined orphan drugs, if implemented, *could add a further century to the pace of orphan drug development*.

The value of orphan and 'ultra-orphan' disease drug treatments is not in question nor do they drive healthcare costs. The total annual cost of treating patients with orphan disease could be conservatively estimated at two trillion dollars with orphan drug costs making up only 4% of this cost.[8] Although orphan drugs make up $68.7 billion in spend per year in the U.S., their ability to alleviate the grave effects of orphan disease is significant.[9,10] Orphan diseases account for $324 billion in lost productivity costs to patients: these are costs that will not be captured in ICER's proposed narrow approach to assessing 'ultra-orphan' and orphan drugs.[11,12] For the 1 in 10 patients who have access, orphan drugs can considerably offset total costs that would have been incurred without an available drug, as measured in healthier Americans living more productive lives. Moreover,

orphan drugs contribute $149 billion to the economy and for every dollar spent in the development of an orphan drug, there is a return of 2.4 dollars to the economy every year.[13] Not only do orphan drugs have a net positive effect on costs and economic return to the economy, but the claim that orphan drugs are putting drug budgets in peril does not hold up against the available evidence.[14,15,16,17,18] With an estimated $750 billion to one trillion in healthcare spend wasted on areas such as unnecessary services and administration costs, ICER has the opportunity to provide insights in areas transformative for U.S. healthcare.[19,20]

ICER's goal is to create a *"more effective, efficient, and just health care system",*[21] however, ICER's proposed approach for assessing orphan drugs could unfortunately do more harm than good to orphan disease sufferers in its current form. The ODA was created because there is a recognition that patients with rare and ultra-rare disease need to be protected with special measures. This 'rule of rescue' is the social contract made to ensure those with orphan and 'ultra-orphan' diseases are protected. ICER has the potential to make a positive contribution to healthcare decision-making by providing information that helps navigate the complex landscape of clinical outcome data. ICER can work to ensure the voices of *all* Orphan Drug Act-defined orphan disease patients are heard and accurately reflected in ICER assessments. To help reach these goals, Amgen specifically recommends the following changes to ICER's proposed framework adaptation for orphan disease:

1. Align the framework with the definitions and provisions in place to protect orphan disease patients
2. Ensure the patient voice is heard and patients are put at the center of assessments
3. Do not attempt to set an arbitrary national threshold for orphan drugs
4. Include costs and cost savings resulting from drugs that are relevant to *all* stakeholders
5. Do not apply the ICER *"Final Value Assessment Framework for 2017-2019"* to orphan drugs: the methodological concerns applied to common disease would be further amplified in orphan disease

ICER's focus should be on guidance in helping to navigate the complex landscape of clinical outcomes. Our major concerns with ICER's proposed approach and our recommendations are further elaborated below.

1) ICER's *de facto* classification of the majority of orphan diseases as common diseases runs counter to the Orphan Drug Act, the U.S. law put in place to protect these patients.

RECOMMENDATION: ICER should not attempt to create a new definition for orphan disease but align to the definition in the 1983 Orphan Drug Act

ICER's proposed 'non-ultra-orphan' designation for orphan disease drugs with 10,000-200,000 patients is in direct conflict with legislation designed to encourage orphan drug development.

- The Orphan Drug Act (ODA) in 1983 clearly defines an orphan disease as those that affect 200,000 or fewer individuals.[22] ICER's proposed definition of ultra-rare disease (*i.e.*, no more than 10,000 patients in the United States) essentially redefines the criteria set out in the Orphan Drug Act and will leave many patients with 'non-ultra orphan' diseases disadvantaged.[23,24,25]
- The epidemiology assessment of orphan disease should be based on the science and historical probability of success and eliminate potential for subjective bias.[26] ICER's definition of 'ultra-orphan' on the basis of a drug that has "*little chance of future expansion of indication or population"* to above 20,000 individuals, is less data based and more a product of estimation or subjective judgment.[27,28] The value of an ODA-defined orphan indication should be divorced from the number of patients a drug treats in another indication.

- Empirical application of the common drug framework to ODA-defined orphan drugs could be disastrous for patients. Every past ICER assessment of an orphan condition has used ICER's common drug framework and this has resulted in a recommendation of 'low value'. Although the panel has been able to overturn this in the past, with ICER's revised value framework for common drugs and 'ultra-orphan' drugs, the panel can no longer make these deliberations. [Appendix, Table 1]
- ICER should consider comments on its proposed approach to assessment of ODA-defined orphan drugs before applying it to assessments. For example, in ICER's finalized scoping document for CAR-T in R/R B-cell ALL, this severe pediatric disease (for which child patients are faced with a shrinking number of drugs for cancer that is no longer responding to treatment) is classified by ICER as a common disease on the basis that CAR-T may at some time in the future be used to treat other diseases. ICER also defines hemophilia A with inhibitors as a 'common disease' despite there being less than 10,000 patients in the U.S.[29] ICER is evaluating treatments based only on estimates of potential treatment population before a drug is approved for that indication.

2) ICER's proposed framework deprives orphan disease patients of a voice in determining value and access to drug treatments.

RECOMMENDATION: ICER should make every effort to ensure a patient centric approach.

The complex nature of measuring value and contextual considerations cannot be captured in ICER's proposed approach to assessing 'ultra-orphan' and orphan drugs.

- ICER's proposed approach to evaluating evidence in 'ultra-orphan' and orphan drugs (the latter defaulting to their common framework), unreasonably penalizes all new 'ultra-orphan' and orphan drugs for lack of evidence at FDA approval. It disregards orphan disease characteristics such as extremely small populations, softer endpoints (which are harder to measure) and difficulties in running clinical programs. [30,31,32] Also, ICER does not make sufficient allowances for assessments to capture the important nuances in orphan and 'ultra-orphan' disease assessment, including society's 'rule of rescue' as well as patients' 'value of hope.[33,34]

ICER's voting process for orphan drugs marginalizes the independent public appraisal committee's contribution, the effect of which is new drugs will be undervalued.

- In the prior process applied to both orphan and non-orphan drugs, the independent public appraisal committee could determine value according to contextual criteria with no quantified quality-adjusted life-year (QALY) range limit. In ICER's 2017-2019 framework, which would also apply to orphan drugs, the committee is no longer empowered to do this.[35] The inflexibility of this system will, by definition, label any 'non-ultra-orphan' intervention that falls $25,000 above the set threshold of $150,000 as 'low' value. This is despite the fact that within 2016 alone all orphan drugs in ICER drug assessments were above $175,000, and six out of eight of the orphan drug regimens tied or received a majority 'intermediate care' value by the public panel (See *Table 1* in the Appendix).[36]

ICER's panel composition does not allow patients or caregivers to vote on treatments that directly affect them.

- Less than 1 in 10 committee members that ICER ask to vote on the value of a drug is a patient, patient caregiver or patient advocacy group and it does not adequately take into account the voice of the patient,

patient caregivers or patient associations. It is important for patients to be able to express the grave and individual burden they experience from orphan disease. [37,38]

ICER has assessed 'ultra-orphan' disease patients as common disease patients in past evaluations.

- In the 2015 High Cholesterol ICER assessment, the cost-effectiveness model for homozygous familial hypercholesterolemia (HoFH), an ICER-defined 'ultra-orphan' condition, was not modeled separately from heterozygous familial hypercholesterolemia (HeFH) because the "*expected number of patients is small [n=300-400 in the U.S.]*." During ICER's Round Table, participants informed ICER that HoFH is "*clearly [an] identified unmet need*" and "*the discussed criteria could be relaxed*".[39] Here, ICER grouped and assessed orphan disease patients together with a different (non-orphan) disease, solely by virtue of small numbers.
- Within ICER's proposed approach to the assessment of orphan and 'ultra-orphan' disease, all 2016 assessed orphan drugs would be classified as 'low value'. Although ICER lacks the mandate to set thresholds and assessments of value, if ICER assessments were to inform access decisions, patients could lose access to new treatments, pay higher co-payments and be forced to try inappropriate treatments prior to new treatments.

3) ICER's proposed willingness-to-pay thresholds are inappropriate to orphan diseases

RECOMMENDATION: ICER should not attempt to set a national price threshold for 'ultra-orphan' drugs and orphan drugs and instead, focus its role on providing guidance based on evidence

ICER's accountability in attempting to re-define orphan disease and set national thresholds for value is subject to substantial contention.

- ICER is assuming an inherent role that exceeds its level of accountability. ICER's attempts to re-define orphan disease, its assertion of nationwide immovable orphan disease and 'ultra-orphan' disease willingness-to-pay thresholds and stated limits across categories of national healthcare expenditure put it in an untenable position, incongruous with the needs of orphan disease patients. This is in stark comparison to those agencies accountable to the U.S. government such as the FDA.[40,41] ICER's best role is articulated by Peter Neumann and Joshua Cohen in: *"ICER should simply calculate and disseminate cost-effectiveness ratios and let its audiences decide whether an intervention represents reasonable value"*.[42]

Subjecting orphan drugs to a value framework with fixed thresholds like ICER's, could be devastating for patients with orphan diseases.

- Many health technology assessment (HTA) groups globally have recognized the ethical, equity and social justice challenges of applying a willingness-to-pay threshold to ODA-defined orphan diseases. Applying a cost-benefit ratio for an orphan disease drug is contrary to an egalitarian/utilitarian approach (maximizing equity for individuals).[43] This approach would prioritize the least costly patients rather than the sickest of patients who lack a sufficient voice in the healthcare system.[44]
- ICER's QALY threshold anchors to 1970 treatment decision standards, not the dynamic environment of 2017.[45,46] Moreover it suggests that the U.S. spend as little as 6 times less per QALY than in 1970.[47] Imposing a willingness-to-pay (WTP) threshold for orphan drugs will not address the needs of the complex U.S. Healthcare System and may jeopardize our societal desire for equity and justice in the insurance system.[48,49]

ICER's proposed 'ultra-orphan' definition, if ever implemented, would make the U.S. one of the most restrictive places in the world for ODA-defined orphan disease sufferers.

- ICER's proposed definition for 'ultra-orphan' disease of less than or equal to 10,000 patients equates to a prevalence of three per 100,000 or less. This excludes any special provisions for orphan disease assessment outside of ICER's 'ultra-orphan' definition. Because if this, if implemented this would make the U.S. the second most stringent country in the world for ODA-defined orphan drugs.[50] Only England's threshold (two per 100,000) is more restrictive than ICER's proposed definition. The impact of implementing this in England has significantly restricted reimbursement, specifically, less than half of approved orphan drugs are reimbursed,[51] and orphan disease patients wait for drugs, on average, over two years.[52,53,54]

The level of certainty around a single threshold is meaningless in orphan disease.

- ODA-defined Orphan diseases typically have very few patients compared to common diseases. Further complicating this, new drugs are often approved at a much earlier stage than other drugs (Phase II). This means that any attempt to set one static price threshold that applies to what is typically a heterogeneous population in orphan disease for which very little is known, would be meaningless at best and at worst could inadvertently harm patients.

ICER's proposed use of willingness-to-pay thresholds based on the quality adjusted life year pose methodological and ethical challenges in orphan disease.

- ICER assessments use a disease outcome measure that can be used across different diseases, the quality adjusted life-year. On technical grounds, QALYs suffer significant shortfalls if applied to orphan disease including (1) they cannot address the heterogeneity in drug options (2) they cannot be derived for very young or very old populations (3) Caregiver QALYs usually are not considered (4) Patients with lower QALYs whose lives are extended will have overall higher/unfavorable incremental cost per QALYs than patients with mild disease.
- ICER's Updated Framework that also applies to all orphan drugs, sets a willingness-to-pay (WTP) threshold of $100,000-$150,000 per QALY. This QALY threshold does not have a scientific foundation. ICER reaches this threshold primarily through two sources which have been extensively criticized: (1) the arbitrary and misapplied WHO "benchmark" of 1-3 times GDP and (2) recent UK work undertaken to set the threshold on the true opportunity cost at the margin of health spending, extensively criticized for its empirical shortcomings.[55,56,57,58,59,60]
- The use of willingness-to-pay price thresholds is not correlated with improved health outcomes and require more research before implementation in the U.S.[61]

4) ICER's proposed assessment approach for 'ultra-orphan' and orphan drugs excludes patient, caregiver and employer costs.

RECOMMENDATION: ICER should include costs and cost savings resulting from drugs that are relevant to all stakeholders

ICER's limitation of costs to the health system undervalues the impact of orphan drugs, and will lead to decisions that shift costs to orphan disease patients, their caregivers, employers and society.

- ICER's choice of costs to include in its proposed value framework goes against the body of academic research in health technology assessment.[62,63,64,65] ICER states that their goal of taking a population perspective is to *"analyze evidence in a way that supports population-level decisions and policies"*.[66] However, ICER's empirical choice of perspective is that of the medical system not the wider population. ICER's inclusion of some costs (medical costs as incurred by insurers) and exclusion of other costs (all other costs including patient costs) marginalizes the financial burden of diseases that patients experience, which could be alleviated by new drugs.

This approach obscures the fact that these costs are not 'saved' but simply incurred by another stakeholder.

- Specific patient groups, their caregivers and employers are likely to be penalized because of this choice of perspective. For many orphan diseases the costs patients and society incur may approach or exceed the health insurer costs. For example, these costs as a percent of medical costs are as high as 94% for cystic fibrosis; 47% for hemophilia, and 216% for Scleroderma patients respectively.[67,68] Out of pocket expenditure in Fragile X in the U.S. have been reported to be as high as $17,476 per patient.[69,70]

5) ICER will apply the "Final Value Assessment Framework for 2017-2019" to all orphan drugs that expand beyond the 10,000 patient definition of 'ultra-orphan' drugs.

RECOMMENDATION: For all healthcare interventions it assesses, ICER should define its role as one of giving *guidance* rather than creating willingness-to-pay price thresholds; ICER should further allow for greater stakeholder inclusiveness (particularly patients) in 1) value determination 2) costs inclusion and 3) the peer-review, transparency and reproducibility of assessments

Amgen has concerns on ICER's Final Value Assessment Framework for 2017-2019 that will also apply to ODA-defined orphan conditions above 10,000 patients.

- ICER's legitimacy and accountability in setting national arbitrary thresholds in the Final Value Assessment Framework for 2017-2019 will continue to be subject to substantial contention. ICER's potential future value lies in a role centered on *guidance.* ICER can inform decisions on value based on key pillars of evidence and its strengths, robust analytics and the identification of areas of uncertainty; and do so with flexibility, inclusiveness, scientific integrity, transparency and patient centricity, in the absence of 'one size fits all' absolutes and thresholds. This would ultimately allow each budget-holder and decision-maker to leverage ICER's insights in making their decisions on value.
- ICER's proposed willingness-to-pay QALY threshold lacks scientific merit and specificity to the complex US healthcare system. ICER's attempt to anchor their lower QALY threshold at $100,000 is irrelevant to the current dynamic U.S. environment. Of note, treatments that have an incremental cost-effectiveness above $175K per QALY will *automatically* be judged 'low value'. This departs from flexible thresholds that leading health economists recommend AND past assessments whereby many drugs that have had

incremental cost-effectiveness ratios above $175K were still judged by the panel as of 'high' or 'intermediate' value.

- ICER's 2017-2019 Value Framework does not address contextual considerations in patient treatment populations. A challenge with the prior version of the Framework that has not been addressed in the current version is that important determinates of value were buried into contextual considerations with less visibility and inability to influence the quantitative analysis.
- In defining and voting on value, ICER's 2017-2019 Value Framework leaves out the patient perspective and that of other key stakeholders in ICER's public appraisal committees. There is the opportunity to further democratize the public appraisal committees (not just the policy roundtable) so that they are composed of more patients, caregivers, patient advocates, clinical experts and manufacturers to help determine the value of new treatments.
- ICER's limitation of costs to the health system will undervalue treatments and lead to decisions that shift costs to patients, their caregivers, employers and society. Payer-borne and monetary costs are only one aspect of healthcare burden.
- ICER's decision-making based on its proposed budget impact model continues to be detrimental to the health needs of patients. Rather than setting national budget impact thresholds that lose relevance in the current multi-payer context, if instead it defined its role as one that is *advisory*, ICER could help articulate to decision-makers what types of elements should be included in their specific budget impact calculations.
- ICER models used for analysis continue to lack transparency, availability and replicability. There is the opportunity to make ICER's and their academic partners' research methods, assumptions, data inputs, and equations available in a completely transparent manner, such that results are fully reproducible by third parties and are reviewed by known experts.

Conclusion

At 25-30 million, the number of patients suffering from orphan disease is a third of the total population with cardiovascular disease, about the same size as the population in the U.S. who are currently living with diabetes, and two times more than those living beyond a cancer diagnosis (many of which are orphan diseases themselves).[71,72,73] Yet despite these large numbers, the drug development constellation is infinitely more complex due to lack of data and information in a field where most of what we have learned about orphan disease in the last five years completely eclipses everything we have learned over the last five centuries. Although we agree with ICER's mission to create a *"more effective, efficient, and just health care system"*,[74] a one size fits all, inflexible approach, such as the one ICER has proposed for orphan drugs, could negatively affect the one in every 10 Americans who are affected by an orphan disease.[75] These patients most need hope, dignity, and respect enhanced by access to valuable drugs for an *equal* chance at achieving a healthy life as everyone who does not suffer from an orphan disease. ICER often refers to European approaches in value assessment and there may be elements that ICER could adopt. Namely, time, stakeholder engagement, extensive research and caution in value framework development. It has taken over 2 years for the European Working Group for Value Assessment and Funding Processes in Rare Diseases to develop principals for assessment.[76] ICER should consider waiting until more research and insights are available to inform an appropriate methodology for the assessment of treatments for orphan disease conditions. In the meantime, ICER should refocus on aligning its role with its stated mission to enable more objective and robust dialogues that inform decisions on 'value' by putting the patient at the center of each assessment.

Appendix

Table 1: 2016 ICER Orphan Condition Assessments With Care Value Votes[77]

ICER Assessment	Orphan Drug Treatment	Long-Term Cost-Effectiveness (at List Price or Net) ($/QALY)*	Care Value – Panel Voting Results		
			Low	Intermediate	High
Primary Biliary Cholangitis	Obeticholic Acid	$473,400	8	6	0
Multiple Myeloma	CFZ+LEN+DEX	$199,982	2	9	0
Multiple Myeloma	ELO+LEN+DEX	$427,607	4	7	0
Multiple Myeloma	IZ+LEN+DEX	$433,794	4	7	0
Multiple Myeloma	CFZ+LEN+DEX	$238,560	2	9	0
Multiple Myeloma	ELO+LEN+DEX	$481,244	6	5	0
Multiple Myeloma	IZ+LEN+DEX	$484,582	5	6	0
Multiple Myeloma	PAN+BOR+DEX	Estimated to provide more QALYs at a lower cost than LEN+DEX as a third line therapy.	4	4	3

** Per ICER's Framework Threshold, >$150K/QALY is recommended as "Low Value"*

Ongoing ICER Assessments of Orphan Disease Conditions (currently being assessed under ICER's Common Framework, as of Q3 2017)

- Emicizumab for Hemophilia A – Draft Scoping Document
- Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value – Draft Scoping Document

References & Endnotes:

[1] Department of Health and Human Services. Office of the Inspector General. Orphan Drug Act Implementation and Impact. 2001. Link
[2] NIH. FAQs About Rare Diseases. Link
[3] Today there are approximately 7,000 orphan diseases affecting 25-30 million Americans, of which there are only 625 FDA designated/approved orphan drugs. 625 compounds are "Designated/Approved" under Orphan Drug Status AND are "Approved for Orphan Indication" under FDA approval status. *Source:* FDA Website. Search Orphan Drug Designations and Approvals. Accessed 28 June, 2017. Link
[4] Global Genes, Allies in Rare Disease. (2015). RARE Diseases: Facts and Statistics. Link
[5] Vernon A, "Examining the link between price regulation and pharmaceutical R&D investment " *Health Economics*. 2005. 14: 1-16.
[6] Researchers including those at Stanford, observe that reducing prices to those in Canada could lead to a 60 percent reduction in research and development (R&D) early stage projects. *Source:* Kutyavina M. "The effect of price control threats on pharmaceutical R&D investments." (2010). Link
[7] This calculation of time needed to find treatments for the remaining orphan indications is modeled by subtracting the current number of orphan drugs from 7000 and then dividing the remaining diseases by the historical average number of orphan drugs developed per year since the Orphan Drug Act of 1983. It assumes that the average rate per year remains constant.
[8] Taking the average annual costs in published data from a systematic review of 77 studies, total annual costs for orphan diseases could be conservatively estimated at $2 trillion dollars per year with orphan drugs making up only 4% of this cost. Very little evidence exists on the total socioeconomic impact of rare disease. The $2 trillion was taken by calculating the average cost per patient per year for rare disease from Angelis *et al.'s* systematic review and then multiplying that cost by the average number of patients in the U.S. with rare disease of 27.5 million. *Source used for calculations:* Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health Policy. 2015 Jul 31;119(7):964-79.
[9] EvaluatePharma. 2017 Orphan Drug U.S. Sales. EvaluatePharma Classic database. 2017.
[10] Huron J. Orphan Drugs Represent 41 Percent of All New Medications. National Organization for Rare Disorders (NORD). Jan. 11, 2017. Link
[11] ICER Institute for Clinical and Economic Review. Obeticholic Acid for the Treatment of Primary Biliary Cholangitis: Comparative Clinical Effectiveness, Value, and Value-Based Price Benchmarks. Evidence Report. July 26, 2016 Link
[12] Drug Options for Relapsed or Refractory Multiple Myeloma: Effectiveness, Value, and Value-Based Price Benchmarks. Final Evidence Report and Meeting Summary June 9, 2016. Link
[13] This calculation was performed by taking the orphan market share of the total share of the pharmaceutical market from Evaluate Pharma forecasts for the U.S. (Accessed May 2017) and its effect on total output and total factor productivity as calculated by the IMPLAN model commissioned by PhRMA. *Source for calculations:* TEConomy Partners; PhRMA. The Economic Impact of the U.S. Biopharmaceutical Industry. Columbus, OH: TEConomy Partners; April 2016. All data used were for 2014, the latest data reported.
[14] Drug budgets as a percent of U.S. total National Health Expenditure (NHE) have not changed since 1960 and orphan drugs as a percentage of this currently represent 2% of all national health expenditure. This is projected to rise 0.5% by 2022 and for this small increase, patients who otherwise would have no other drug have a chance to live a healthy and productive life. *Source:* Catlin AC, Cowan CA. History of Health Spending in the United States, 1960-2013.
November 19, 2015. Link
[15] CMS Proj2016 Tables: Table 11 Prescription Drug Expenditures.
[16] CMS Proj2016 Tables: Table 01 National Health Expenditures and Selected Economic Indicators.
[17] Evaluate Pharma U.S. Orphan Drug Total Sales 2017 and 2022.
[18] We strongly support ICER's goal of helping healthcare become more sustainable but recommend that ICER look to macroeconomic healthcare expenditure drivers whereby National Health Expenditure, by the estimates of CMS is affected by prices of medical services (supply-side drivers) and use and intensity of medical goods and services (demand side drivers) with the prices of medical services projected to drive expenditure over the next 8 years. Concentrating on orphan drug expenditure will have no impact on overall healthcare expenditure, nor will it help public or private insurers materially contain even short-term healthcare expenditures. Instead this will result in a deleterious effect of loss of life and welfare for very vulnerable individuals, half of which are children, who have had the unfortunate consequence of being afflicted with an orphan disease. *Source:* Centers for Medicaid and Medicare. National Health Expenditure Data. Link
[19] McGinnis JM, Stuckhardt L, Saunders R, Smith M, editors. Best care at lower cost: the path to continuously learning health care in America. National Academies Press; 2013 Jun 10.
[20] Sahni N, Chigurupati A, Kocher B, Cutler DM. How the U.S. Can Reduce Waste in Health Care Spending by $1 Trillion. Harvard Business Review. October 13, 2015.
[21] ICER Website. Accessed August 2017. Link
[22] Department of Health and Human Services. Office of the Inspector General. Orphan Drug Act Implementation and Impact. 2001. Link
[23] U.S. Food and Drug Administration (FDA). The Orphan Drug Act. Relevant Excerpts (Public Law 97-414, as amended). Last updated August 2013. Link
[24] Breakthrough designation – Congress directed the FDA to establish another program to expedite the development and review of new drugs under Section 902 of the July 9, 2012 Food and Drug Administration Safety and Innovation Act. Congress passed the Orphan Drug Act (ODA) in 1983 in order to promote the development of drugs for indications like B-ALL and clearly define orphan drugs as drugs that treat conditions that affect

200,000 or fewer people in the U.S. Priority Review was developed under the 1992 Prescription Drug User Act (PDUFA) to ensure that overall attention and resources be given to drugs which treat serious conditions.

[25] The goal of the ODA is to provide incentives for manufacturers to develop drugs in conditions that impact a small number of patients as defined as 200,000 or fewer people in the U.S.. Benefits such as reduced "user fees", tax deductions for clinical trials, grants and market exclusivity are necessary to encourage research but have not been sufficient to encourage significant growth and development in the pediatric oncology space.

[26] The epidemiology for many orphan and 'ultra-orphan' diseases is not well known and can vary significantly in estimated numbers.

[27] FDA. Developing Products for Rare Diseases & Conditions. FDA Website. Accessed 27 June, 2017. Link

[28] 1984 population was 235.82 million; 2017 population as of 1 June was 325.15 million equivalent to a 38% increase over this 1984-2017 period. *Source*: U.S. Census Bureau. U.S. population by year accessed on Link and Link

[29] ICER states "*while the population of hemophilia A patients in the US with inhibitors is likely much less than 10,000, and treatment with emicizumab offers potential major gains in quality of life, future expansion of use to the broader population of patients with hemophilia A could extend the size of the treated population to above 20,000 individuals. As such, we plan to evaluate emicizumab under the usual ICER value assessment framework." Comment:* Treatment and value estimation of drugs for Hemophilia A patients should be divorced from whether a drug will help other patients. This helps keep the 'protected' status of these orphan disease patients. By subjecting the new drug to a common disease framework that is less likely to lead to a positive outcome if leveraged by decision-makers. *Source:* Institute for Clinical and Economic Review (ICER). Emicizumab for Hemophilia A – Draft Scoping Document. ICER. 2017 Sept 11. P. 3.

[30] Orphan disease research is characterized by difficulty in clinical trial design and recruitment and training of clinical scientists. Gold-standard randomized, double-blind, placebo-controlled trials cannot always be conducted in orphan diseases requiring alternative study designs. For orphan drugs to demonstrate efficacy in studies with a very small number of patients, drugs may be required to show a bigger drug effect than in large studies. *Source:* Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, Nguyen T, Paulus K, Merkel PA. Clinical research for rare disease: opportunities, challenges, and solutions. Molecular genetics and metabolism. 2009 Jan 31;96(1):20-6.

[31] Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. Jama. 2011 Jun 8;305(22):2320-6.
Link

[32] Wästfelt M, Fadeel B, Henter JI. A journey of hope: lessons learned from studies on rare diseases and orphan drugs. Journal of internal medicine. 2006 Jul 1;260(1):1-0.
Link

[33] 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. 2012 Apr 1;31(4):676-82.

[34] Shafrin J, Schwartz TT, Okoro T, Romley JA. Patient versus physician valuation of durable survival gains: implications for value framework assessments. Value in Health. 2017 Feb 28;20(2):217-23.

[35] ICER. Institute of Economic and Clinical Review. Overview of the ICER value assessment framework and update for 2017-2019. ICER. June 22 2017. Link.

[36] Based on an analysis of all ICER assessments in 2016 from ICER reports and summary findings.

[37] This is important as orphan diseases are devastating to patients and caregivers due to their rapid progression, reduced life expectancy, and significant disability, often manifesting in infants and young children. *Source:* de Vrueh R, Baekelandt ERF, de Haan JMH, WHO Background Paper 6.19 Rare Diseases. Link

[38]. Orphan diseases put an extensive economic burden on patients and caregivers curtailing their ability to work *Source:* Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health Policy. 2015 Jul 31;119(7):964-79.

[39] Institute of Clinical and Economic Review (ICER). PSK9 Inhibitors for Drug of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks: Final Report. ICER. 2015 Nov 24. Link

[40] For example, when the FDA makes a decision to approve a new drug, it is directly accountable to the U.S. government with extensive regulations, audits and procedures that ensure that its evaluations are credible, consistent, transparent and as accurate as the available information allows. *Source:* Miller KL, Woodcock J. Value Assessment in the Regulatory Context. *Value in Health* (2017) 20:296-298.

[41] ICER sets out the goal to "*inform decisions that are aimed at achieving sustainable access to high-value care for all patients*", yet setting of QALY thresholds goes beyond 'informing' to assuming the role of the decision-maker itself on care that it neither delivers, funds nor receives. Setting new definitions for orphan disease subjects patients to artificially created barriers that go against legislation put into place by society to protect patients with orphan diseases.

[42] *But as with ICER's use of a budget cap, the group's imposition of a threshold is itself the problem, in the sense that their role is that of the evaluator not decision maker. In other words, who is ICER to determine what tradeoffs payers and their enrollees are willing to make? Those judgements should only be rendered by budget holders (i.e., payers and their enrollees).* COMMENTARY ICER's Revised Value Assessment Framework for 2017–2019:A Critique. Pharmacoeconomics. Published Online 8 August, 2017.

[43] Many of these HTAs have special processes and special funding mechanisms for orphan diseases. For example, Sweden considers the 'human dignity principle', which essentially combines the recognition that all citizens should be treated equally, and the "needs-solidarity principle" which strives to optimize clinical benefit based on individual patient need. *Source:* Zelei T, Molnár MJ, Szegedi M, Kaló Z. Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries. Orphanet journal of rare diseases. 2016 Jun 4;11(1):72..

[44] Kaczynski L, Serafin B, Przada-Machno P, Kaczor M. Is the cost-effectiveness threshold cost-effective in cancer therapy? JPOR 2015:2.6. Link

[45] Kidney dialysis is the original basis for the $50,000 QALY threshold from the 1970's. Demonstrating the inappropriateness of this lower threshold, in 2009, US researchers derived a QALY range for kidney dialysis averaging $129,090 per QALY with a top range of $488,360 for sicker patients. *Source:* Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. Value in Health. 2009 Jan 1;12(1):80-7. Link. In the ensuing 8-10 years since this analysis, the QALY range is likely to be even higher.

[46] A 2008 study that derived a US QALY threshold empirically from researchers at Yale calculates a range of $118,000 to $264,000 cost per QALY: this upper range is likely more appropriate for the US, as it represents patients that are insured. *Source:* Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care 2008;46:349-356).

[47] A search reveals: 50k USD in 1970 is 325k USD today - 150k USD would be around 1 million. Since 1970 price levels in the whole economy have increased >6x. Using the same threshold which was applied in 1970 means that ICER is imposing a value threshold which is 6x less than in 1970.

[48] Drummond MF. Challenges in the economic evaluation of orphan drugs. Eurohealth. 2008;14(2):16-7.

[49] Orphan drugs have highly variable and unique circumstances specific to each disease (*e.g.*, small study population, quantification of quality of life benefit, rarely measured spillover effects in families and caregivers, variation in cost-offsets, burden of illness, accelerated approval, *etc.*). *Source:* Nielsen S, Shields G, Britton J, Cote S. Gaudig M. Challenges for Assessing the Economic Value of Orphan Drugs – a Literature Review of Current and Alternative Approaches. ISPOR Abstract, ISPOR 18th Annual European Congress, 7-11 November 2015, Milan, Italy.

[50] U.S. Census (Accessed 8-7-2017)

[51] Office of Health Economics. Comparing Access to Orphan Medicinal Products (OMPs) in the United Kingdom and other European countries. March 2017. Link

[52] Equity and Access: Making the UK a Rare Disease Leader. (2017) Commissioned and funded by Shire Pharmaceuticals and developed in collaboration with an external steering group. Link

[53] In February of 2017, NICE rejected the use of Alexion's Kanuma to treat infants, children and adults with the rare inherited genetic disorder lysosomal acid lipase deficiency (LAL-D). Infants with LAL-D normally do not live to see their first birthday without treatment. PharmaTimes "NICE rejects Alexion's rare disease therapy Kanuma". Link

[54] In September of 2016, NICE excluded Alexion's Strensiq for treatment for those with juvenile-onset form of HPP. While the juvenile and adult-onset forms of HPP have much lower mortality rates than those appearing in infancy, later forms are often linked with debilitating bone deformities. PharmaTimes "NICE backs restricted use of Alexion's Strensiq" Link

[55] Robinson LA, Hammitt JK, Chang AY, Resch S. Understanding and improving the one and three times GDP per capita cost-effectiveness thresholds. Health Policy and Planning. 2016 Jul 24:czw096. Link

[56] Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost–effectiveness of interventions: alternative approaches. Bulletin of the World Health Organization. 2015 Feb;93(2):118-24. Link

[57] Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, Sculpher M. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health technology assessment. 2015:1-542. Link

[58] Claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, Devlin N, Smith PC, and Sculpher M. Methods for the estimation of the NICE cost effectiveness threshold. CHE Research Paper 81. Revised following referees' comments. York: Centre for Health Economics, University of York. 2013. Link

[59] Barnsley P, Towse A, Sussex J. Critique of CHE research paper 81: methods for the estimation of the NICE cost effectiveness threshold. 2013. Link

[60] This UK work (*Op. cit*, Claxton et al., 2013) which has also been extensively criticized for its empirical shortcomings, derived a threshold for the UK given an assumed budget and health production for that country's single payer National Health System. ICER has then accepted further recommendations that such a discovered threshold can be extrapolated to other countries (and, importantly, healthcare systems) by anchoring it to 1-2 times GDP per capita (adjusted for purposing power parity).

[61] One analysis of cancer reports that countries utilizing QALY thresholds have with correlated lower survival rates. *Source:* IMS. Impact of cost-per-QALY reimbursement criteria on access to cancer drugs. IMS Institute for Healthcare Informatics. Dec. 2014.

62 Cost-Effectiveness in Health and Medicine. Edited by Newmann PJ, Sanders GD, Russell LB, Siegel JE, Ganiats TG. Oxford University Press, New York 2017. Link

[63] *"A second problem is ICER's use of a narrow healthcare perspective for its base-case CEA, which the organization calls the most relevant viewpoint for the public and private decision-makers. Such a perspective may make sense for payer audiences (particularly private ones), but, as highlighted recently by the Second Panel on CEA, it omits potentially important elements (e.g., impacts on productivity and caregivers)." Source:* Neumann PJ, Cohen JT. COMMENTARY ICER's Revised Value Assessment Framework for 2017–2019:A Critique. Pharmacoeconomics. Published Online 8 August, 2017.

[64] Weinstein *et al.* 1996 state that "*The major categories of resource use that should be included are costs of health care services; costs of patient time expended for the intervention; costs associated with caregiving (paid or unpaid); other costs associated with illness, such as child care and travel expenses; economic costs borne by employers, other employees, and the rest of society, including so-called friction costs associated with absenteeism and employee turnover; and costs associated with nonhealth impacts of the intervention, such as on the educational system, the criminal justice system, or the environment.*" *Source:* Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. Jama. 1996 Oct 16;276(15):1253-8. Link

[65] Neumann PJ, Kamal-Bahl S. Should Value Frameworks Take A 'Societal Perspective'? Health Affairs Blog. September 6, 2017
66 Institute of Clinical and Economic Review (ICER). *op. cit.* p.2 Link
[67] Pauly M. The economics of cystic fibrosis. In: Lloyd-Still JD, editor. Textbook of cystic fibrosis. Boston: John Wright PSG Inc.; 1983. p.465–76.
[68] Schramm W, Royal S, Kroner B, Berntorp E, Giangrande P, LudlamC, *et al.* Clinical outcomes and resource utilization associated with haemophilia care in Europe. Haemophilia 2002;8(1):33–43.
[69] Ouyang L, Grosse S, Raspa M, Bailey D. Employment impact and financial burden for families of children with fragile X syndrome: findings from the National Fragile X Survey. Journal of Intellectual Disability Research 2010;54(10):918–28.
[70] The lack of cost-of-illness evidence in orphan diseases raises a significant concern that patient out of pocket and indirect costs from lost workdays (which can be substantial to patients and their caregivers) will not be considered due to the lack of evidence available. Only the cost of new drugs, not the costs that they take out of the system are included in ICER's assessments such that economic burden that patients experience is only seen from a narrow aperture of budget impact.
[71] American Heart Association, "At-a-Glance," Link
[72] National Diabetes Statistics Report, 2014. Link
[73] NIH. FAQs About Rare Diseases. Link; National Cancer Institute, Cancer Statistics, Link
[74] ICER Website. Accessed August 2017. Link
[75] *Op. cit.* Global Genes, Allies in Rare Disease. 2015.
[76] Annemans L, Aymé S, Le Cam Y, Facey K, Gunther P, Nicod E, Reni M, Roux JL, Schlander M, Taylor D, Tomino C. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL). Orphanet journal of rare diseases. 2017 Mar 10;12(1):50.
[77] Based on an analysis of all ICER assessments in 2016 from ICER reports and summary findings.

Anthem

Submitted electronically via: publiccomments@icer-review.org

September 25, 2017

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

Re: ICER's Proposed Value Assessment Framework for Treatments That Represent a Potential Major Advanced for Serious Ultra-Rare Conditions

To Whom It May Concern:

Anthem is working to transform health care with trusted and caring solutions. Our health plan companies deliver quality products and services that give their members access to the care they need. With over 74 million people served by its affiliated companies, including more than 40 million within its family of health plans, Anthem is one of the nation's leading health benefits companies. For more information about Anthem's family of companies, please visit www.antheminc.com/companies.

In Anthem's role as a payer we share the Institute for Clinical and Economic Review's (ICER's) commitment to researching and evaluating drugs and other medical services through a value-based lens. Anthem strives to improve the health of our members while providing access to affordable health care. As part of that effort, Anthem is committed to the ongoing evaluation of the safety and efficacy of drugs and therapy regimens. In response to ICER's *Proposed Value Assessment Framework for Treatments That Represent a Potential Major Advanced for Serious Ultra-Rare Conditions,* Anthem would like to share several high-level comments:

- **Treatments for rare diseases and ultra-rare diseases should be held to equitable standards of evidentiary and value assessment, with interpretative context being applied *after* analysis**. – ICER should not change its requirement that net health benefit of new treatments in ultra-rare diseases be evident from the published medical literature. However, when traditional trial designs are not feasible due to the small population, methodological considerations need to be applied when interpreting the outcomes of the analysis. There may be a need to establish different clinical thresholds for certain subpopulations of patients. In particular, as the size of a population diminishes, it becomes essentially impossible to establish safety through RCTs. Alternative methodologies will be needed to monitor for safety signals during and after the regulatory approval process. When safety concerns are raised during analysis, it is even more critical in the case of rare and ultra-rare conditions, to further evaluate the proposed treatment. Evidence must still establish efficacy and it is expected that appropriate trial designs will be developed to address efficacy and effectiveness in rare and ultra-rare populations.

- **When possible, well-designed randomized control trials (RCT) must continue to be the gold standard for rigorous systematic review of high-quality evidence.** – The prevalence of rare or ultra-rare conditions makes study design difficult for RCTs. In practice, clinical trials often rely on small specified patient cohorts and stakeholders must reach reasonable conclusions on the best evidence available. Incorporating real-world evidence (RWE) in an era of increased interoperability and clinical data sharing can support post-market surveillance efforts more broadly. When RCTs are not possible, RWE can enable more precise decision making and increase the applicability of the results to make them more impactful to respective populations. Non-RCT sources including manufacturer data or patient reported outcomes must be peer-reviewed and published in credible scientific journals, or formally submitted to the FDA and made publicly available. If ICER decides to incorporate additional sources of non-RCT data, respective limitations should be duly noted, and endpoints evaluated by ICER must be pre-specified by the researchers and not the result of secondary or tertiary post hoc analyses. Failure to acknowledge the present limitations could result in spurious associations and false or misleading results.
- **Further clarification (including rationale behind the thresholds cited) of incidence and prevalence parameters of orphan disease definition is needed, particularly for those conditions where clinical phenotype is heterogeneous and disease severity varies widely. –** Clinical efficacy is paramount for our members and any "major gain" as specified by ICER should be defined more clearly. Furthermore, it would be beneficial to understand the potential varying degrees of validity of ICER's present assumptions (pertaining to surrogate endpoints). Analysis could be conducted to examine various parameters of uncertainty with these assumptions. In addition, proposed adaptations to Willingness to Pay (WTP) and Quality-Adjusted Life Year (QALY) thresholds seem to minimize the already significant incentives associated with the ODA for manufacturers, such as waiving user fees, grants for drug development, fast-track approvals, major tax credits and market exclusivity. ICER should consider the potential effects associated with significantly increasing QALY and how that may alter incentives amongst manufacturers, given that ICER's mission is defined by societal affordability considerations.
- **Long-term systemic affordability must continue to be a critical factor when examining the potential impact of new and/or existing drugs, devices and procedures.** – High priced technologies present an ever-increasing impact on the financial stability of the healthcare system, with costs ultimately being born by consumers through either higher premiums or a potential need for increased taxes to fund government programs. Outcomes-based analysis must consider that drug, device and procedure prices are reflected in overall healthcare costs. Seven of the top ten drugs sold on the market by total revenue in the United States in 2015 were classified as orphan drugs[i], affirming ICER's analysis framework as an even more critical piece of the long-term conversation on pharmaceutical policy, as decision makers further study value and cost-effectiveness evaluations. Modeling should consider the scope of the potential patient population and the potential for the drugs', devices' or procedures' effectiveness to expand to larger populations through both on label and off label uses in order to properly assess potential impacts both short and long term – as noted above, the volume of people affected impacts affordability. The introduction of Hepatitis C drugs such as

Harvoni and Sovaldi into the market is one example which shocked the budgets of both private and public payers given the vast applicability to a large population size.

We strongly encourage organizations like ICER to conduct ongoing value assessments of treatments for new market entries to ensure that drugs, devices and procedures are not resetting the market in a way that causes untenable cost burdens on patients and payers. Society must consider that health care resources are fixed when budgetary resources are finite, and thus any funding for ultra-rare diseases will result in less funding for more common diseases that may affect larger population sizes. The societal goal is to try to tie together rare conditions where there may not be adequate incentive to develop a drug. The healthcare system would pay a premium where the incremental value is sufficient, the population is small and the incentive for drug development is small. If the incremental value is small, society should not pay a premium.

Lastly, taxpayers have a stake in the development of these drugs; critical grant funding allocated to manufacturers facilitates research to support the development of treatments for rare and ultra-rare diseases. A present disconnect between the definitions of "orphan drug" and "orphan disease" places the integrity of the Orphan Drug Act (ODA) at risk. We encourage rigorous review of the incentives present within the spirit of the legislative intent of the Orphan Drug Act to strengthen and uphold its original mission – "to stimulate the development of drugs for rare diseases".

At Anthem our ultimate commitment is to safeguard the balance of value and efficacy of healthcare services for all of our members and better improve health outcomes.

***

We look forward to working with you as you move through the review process.

Sincerely,

John Whitney, MD, VP Medical and Clinical Pharmacy Policy

John Yao, MD, Staff VP Medical Policy & Technology Assessment

Geoffrey B. Crawford, MD, MS Medical Director – Office of Medical Policy and Technology Assessment

Vicki Fisher, Director, Clinical Analytic Strategies

Jeff White, Staff VP Clinical Pharmacy Services

[i] Tribble, Sarah Jane, and Sydney Lupkin. "Drugs For Rare Diseases Have Become Uncommonly Rich Monopolies." *NPR*. NPR, 17 Jan. 2017. Web.

September 25, 2017

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

Re: Comments on Proposed Ultra-Orphan Adaptations to the ICER Value Framework

Dear Dr. Pearson:

On behalf of BioMarin, we appreciate the opportunity to comment on the Institute for Clinical & Economic Review's (ICER) proposed ultra-orphan adaptations to its current value framework. BioMarin has 20 years' experience as a global leader in developing innovative therapies for a small number of patients with life-limiting ultra-rare and rare genetic diseases. Each of our five Food & Drug Administration (FDA) approved products are novel and are the only drug therapies indicated to treat their respective high-burden diseases. We expect each therapy will be utilized only in the single disease state reflected in the FDA label.[1] As one of very few manufacturers focusing exclusively on ultra-rare and rare disease, we hope our perspective will be helpful as ICER finalizes its ultra-orphan adaptations.

ICER's value framework (revised July 2017), is designed for disease states with larger patient populations.[2] ICER's proposed changes for these therapies, including an increased threshold for willingness to pay at $500,000 per quality-adjusted life year (QALY) and option for cost-consequence analysis, increases flexibility in the existing framework for ultra-rare and rare therapies. We appreciate ICER's proposal to more adequately capture the full set of components that define value for these therapies, but we maintain that key aspects of health technology assessment (HTA) and even modified HTA frameworks often fail to provide a clear picture of this value. A framework that hinges on cost effectiveness is not appropriate to evaluate ultra-rare therapies.[3]

We understand from our extensive experience with value assessment in ex-US markets that incorporating clinical benefit and cost to determine value into decision-making has undeniable challenges. Other countries have acknowledged the limitations to producing accurate and usable ultra-orphan drug HTAs, including use of distinct review processes in England, Scotland, and Wales. One challenge is the fact that the relevant evidence base often relies on smaller studies of a lower quality of evidence, due to the related challenges of conducting clinical research and limited availability of data on natural history of disease. Thus, greater flexibility to consider lower quality of evidence, including case studies and small case series of few patients, is critical, and expectations for quality of evidence should be moderated accordingly.

[1] Note: For example, the expected prevalence of CLN2 disease, relevant for newest therapy, Brineura, is approximately 250 in the United States. Due to the nature of enzyme replacement therapy, we do not anticipate Brineura adequately treating patients who are not TPP1 enzyme deficient.
[2] Institute for Clinical & Economic Review. Final Value Assessment Framework for 2017-2019. Available at https://icer-review.org/final-vaf-2017-2019/.
[3] Schlander M, Garattini S, Kolominsky-Rabas P, Nord E, Persson U, Postma M, Richardson J, Simoens S, de Solà-Morales O, Tolley K, Toumi M Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement. J Mark Access Health Policy. 2016.

As ICER has acknowledged, critical factors that define value for ultra-orphan diseases include the level of unmet medical need for patients and other contextual considerations and benefits.[4] Patients often require intensive care which can place a significant burden on healthcare and caregiver resources.[5] A complete assessment of value must consider benefit for patients and their caregivers, as well as physician input and societal perspective.

A holistic view is critical in any determination of a therapy's value, including from the patient perspective. Patients and their families continue to experience significant unmet medical needs in ultra-rare and rare disease.[6] These diseases tend to be serious, life-threatening, and lack approved therapy. The emergence of a therapy can have potential for significantly improved standard of care as well as understanding of the disease state, longer-term health outcomes, and appropriate patient management. At BioMarin, we recognize the importance of the patient voice and incorporate the patient perspective throughout the lifecycle of our products, from early development to marketing. Healthcare stakeholders have recognized the importance of incorporating patient voice in product development as well as regulatory decision-making. For example, legislation recently signed into law[7] requires FDA to consider patient information and perspective in drug approval decisions. The importance of these factors to any determination of a therapy's value especially for ultra-rare diseases should not be undermined. We encourage ICER to closely consider these factors and incorporate them into any determination of value that informs healthcare stakeholders' decisions.

We encourage ICER to first and foremost consider the benefits that therapies for ultra-orphan disorders bring to patients. ICER should focus on the other benefits and contextual considerations associated with ultra-rare and rare therapies; though difficult to quantify, these are several of the most critical factors that determine a therapy's value. We urge ICER to finalize any changes in a transparent manner and to apply the framework judiciously with adequate input from a range of healthcare stakeholders, including patients and families.

Sincerely,

Beth Rader
Senior Director, Market Access
BioMarin Pharmaceutical Inc.

[4] Institute for Clinical & Economic Review. Orphan Drug Assessment: Final Meeting Report and Proposed Framework Changes. Available at https://icer-review.org/material/odaps-proposed-changes/.
[5] Schieppati A, Henter JI, Daina E, Aperia A, Why rare diseases are an important medical and social issue. Lancet. 2008;371:2039–41.
[6] Approximately 7,000 different types of rare diseases have been discovered so far and an approved treatment exists for just 5% of them (See The Global Genes Project, "RARE Diseases: Facts and Statistics," Available at http://globalgenes.org/rare-diseases-facts-statistics/). In addition, fewer than 10% of rare disease patients receive disease-specific treatment due to delayed diagnoses, limited access to resources, and lack of specific therapies (See Melnikova I. Rare diseases and orphan drugs. Nat Rev Drug Discov. 2012;11(4):267–8).
[7] See 21st Century Cures Act (P.L. 114-255) and FDA Reauthorization Act (P.L. 115-52).

Biotechnology Innovation Organization

September 25, 2017

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: ICER's Proposed Revisions to its Value Framework for Treatments for Ultra-Rare Diseases

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) "Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions" (modified Framework).[1] 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 healthcare expenditures due to fewer physician office visits, hospitalizations, and surgical interventions.

BIO appreciates the opportunity to comment on these proposed revisions. Patients living with rare diseases often experience significant unmet medical need due to the lack of knowledge about how these diseases are caused or inherited and their progression. That those suffering from rare diseases are predominately children raises issues around how society prioritizes and develops treatments for these conditions. We believe there are significant challenges in reconciling existing population-level value assessment methodologies with the varied healthcare contexts and deeply personal patient-level treatment decisions faced by patients afflicted with rare diseases, their families, and their clinicians. For a number of reasons, applying a patient-centric lens when considering the value of treatment is especially important when considering rare diseases:

[1] July 25, 2017. Available at: https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf

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- The health consequences of rare diseases can often be debilitating or deadly;

- The manifestation of the burden for a given disease is often unique to individual patients and their caregivers; and

- The healthcare needs of patients with rare diseases are underrepresented in healthcare policy discussions and treatment delivery systems, which are typically focused on broader population healthcare.

Given these factors, we strongly believe that the application of a population-based approach (such as the cost per quality-adjusted life year, or QALY) to value treatment for rare diseases is fundamentally misguided because the assessment principles of population-based approaches inherently under-value the unique considerations appropriate for rare diseases. As such, we believe that a new and innovative approach to value rare diseases should be created; one that focuses wholly on the value of innovation to the individual, their caregivers, and society.

As we noted in our second comment letter on ICER's proposed revisions to its Value Framework earlier this year, we continue to support the assessment of medicines that treat rare and ultra-rare diseases outside of ICER's standard Value Framework. **However, we are concerned that the revisions ICER now proposes would not result in meaningful differences in the way ICER's assessments are presented and interpreted by patients, health plans, consumers, and policy makers.**

Although some of the proposed changes have the potential to capture the nuance and complexity of these conditions, the underlying Framework continues to rely on a methodology that conflates value, short-term affordability, and budget impact. A budget impact threshold has no bearing on clinical decision-making, and as we have commented previously, could mislead those reviewing these assessments into thinking that the arbitrary spending caps put forth by ICER could improve patient care or reduce healthcare costs. In fact, research has shown the negative impact of such caps on patient access to needed medicines, incentives for future innovation, and market efficiency.[2]

We also continue to object strongly to the use of the QALY as the foundational metric of ICER's assessments. Methodological concerns with using QALYs in a decision-making setting are well documented but present unique problems when assessing the value of medicines that treat rare diseases.[3] A QALY distills the entire patient experience for a particular medical intervention into one number. But as the field of personalized medicine advances and interventions can be tailored down to the level of a patient's own genetic code, any rationale for

[2] For example, see Ciarametaro, M., S. Abedi, A. Sohn, C. Fan Ge, N. Odedara, and R. Dubois. 2017. Concerns Around Budget Impact Thresholds: Not All drugs are the same. *Value Health* 20(2):230-233. See also Thomas A. A., and J. A. Wernon. 2007. The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions. *MDE Managerial and Decision Economics* 28:293-306.

[3] See: Measuring Value in Medicine: Uses and Misuses of the QALY. Partnership to Improve Patient Care. June 2017. Available at: http://www.pipcpatients.org/resources/white-paper-uses-and-misuses-of-the-qaly-ethical-issues-and-alternative-measures-of-value

using QALYs in clinical decision-making fails as a framework. ICER's continued use of the QALY in both its general Value Framework and in its modified Framework for medicines that treat ultra-rare diseases will undermine the goals of personalized medicine.

We encourage ICER and all stakeholders engaged in value assessment to explore less narrow and restrictive approaches to quantifying the value of medicines that accounts for the unique characteristics of the patients and diseases being considered. There is no "one size fits all" definition of value, particularly as it relates to treatments for rare diseases. Value assessment tools that put forward arbitrary constraints as objective fact or employ opaque methodologies harm, rather than aid, the ongoing conversation around value.

In addition to our comments around ICER's approach to value assessment generally, we offer the following recommendations related to the specific changes the Institute is proposing when assessing the value of treatments for ultra-rare diseases.

Sections 1.1 and 1.2 – Criteria and process for use of the modified framework

ICER proposes to "consider" using its modified framework for treatments that are noted as a "potential major advance for a serious ultra-rare condition" when three criteria are met: (1) the treatment envisages a population of fewer than 10,000 individuals, (2) there is little chance of future expansion of indication or population that would extend the size of the treatment population above 20,000 individuals, and (3) the treatment potentially offers a major gain in improved quality of life and/or length of life.

As proposed, we believe these criteria are arbitrary and overly rigid – failing to capture the profound complexity and nuance that exists in the field of rare diseases. Although ICER discusses how other stakeholders both inside and outside of the United States have attempted to define rare and ultra-rare disease, the Institute offers no justification or rationale for why a patient population of 10,000-20,000 should be the range of what is considered "ultra-rare." As no statutory authority or regulatory body in the United States has yet developed a definition of "ultra-rare," **ICER should either defer to using its modified Framework for medicines that meet the statutory definition of "rare disease or condition" as established by the Orphan Drug Act (200,000 individuals in the United States) or abandon strict number limits altogether and instead adopt a more dynamic decision-making process that reflects the complexity of diseases in this space.**

For example, ICER has acknowledged that new treatments will necessarily lead to an increase in disease screening and accelerate diagnoses through greater patient and physician education. It is difficult to know with a great degree of certainty beforehand how much this interaction will change the patient population for a given medicine, making strict numerical constraints on how much the intended patient population can grow while still being considered "ultra-rare" inappropriately limiting.

Flexibility in defining ultra-rare diseases is needed not just because of issues of disease prevalence, but also disease heterogeneity and complexity. ICER's initial ceiling of 10,000 patients in the United States is far too low when considering many rare diseases can be caused by

one of a number of different genetic mutations. Together, the population of patients with a particular condition may exceed 10,000 individuals based on sub-categories within a disease state – thus falling outside of ICER's proposed definition of an ultra-rare disease. However, within that group the mechanism causing the underlying condition may vary greatly, with each requiring a different therapeutic approach.

In deciding whether or not to apply this modified framework to a particular intervention, we also believe the proposed language is ambiguous – illustrating how ICER's current approach to value assessment does not fully account for the range of value propositions for a given medicine. ICER says it will "consider" using a revised framework when its three criteria are met. This implies that ICER could, at its discretion, elect not to utilize the modified framework even when its three criteria are met. Section 1.1 also notes that treatments will be evaluated using these criteria when the treatment presents a "potential major advance." This phrase is highly subjective. Patients, clinicians, payers, and the public may all have differing opinions about what constitutes a "potential major advance" in a particular disease area. Holistic value assessments should not disregard one stakeholder's concept of value in favor of another's. We recommend ICER develop and publish clear criteria around the characteristics that a treatment would have to meet in order to be considered a "potential major advance" in a given therapeutic area. At a bare minimum, ICER should be upfront and transparent about the specific methodologies used to decide when a treatment may offer a potentially major advance.

BIO agrees that treatments for ultra-rare diseases with near-term market potential in non-orphan populations are different from pure ultra-orphan products. We have grave concerns, however, with ICER's broad "solution" of an ICER determination that a product has "little chance of expansion" as it creates uncertainty and injects far too much speculation. **ICER should not conduct assessments, through the modified Framework or otherwise, for treatments addressing ultra-rare conditions for which no alternative FDA-approved treatment exists, unless the manufacturer or patient groups request an assessment in response to access constraints.** This should also apply to situations in which there are symptomatic, but no disease-modifying therapies available on the market.

ICER's stated goal in each of its assessments under the modified Framework is to "provide specific context and additional information so that decision-makers will be adequately informed of the distinctive character of the evidence and the broader considerations that should be part of policy decisions regarding treatments for rare conditions." ICER's framework of willingness-to-pay thresholds and panel votes to categorize treatment value may further its goals where providers, patients, and payers face a decision among treatment options with similar efficacy profiles. However, for patients seeking access to the only FDA-approved or disease-modifying therapy for an ultra-rare disease, the "value" calculation morphs to deciding whether the improved quality and/or duration of their lives is worth the money within an artificial construct in direct conflict with the "policy decisions" that have been codified for Medicare, Medicaid, and commercial issuers. It also would stand in contrast to existing coverage standards under many federal programs that require coverage of therapies that mitigate or halt the

progression of the underlying disease even when therapies that treat only the symptoms of the disease are also available.[4]

We also recommend ICER resolve ambiguity around the terminology it uses when discussing diseases assessed under the modified Framework. In introductory language, the Institute focuses on "rare" conditions and explains why additional methods are required for assessing the value of therapies targeted for rare conditions. In Section 1.1 however, the Institute changes course and asserts that adapted methods are not necessary for the majority of orphan drugs. Elsewhere in the report, ICER appears to use the terms "orphan," "rare," "ultra-rare," and "serious ultra-rare" interchangeably – leading to confusion. ICER should define and use consistent terminology throughout the finalized modified Framework.

Section 2.1 – Standards of evidence

ICER proposes to not change its standards of evidence or Evidence-Based Medicine (EBM) rating matrix when assessing treatments under the modified Framework. It would instead discuss relevant difficulties in generating evidence for treatments with very small patient populations (randomized controlled trial challenges, long-term data on safety, and durability of clinical benefit).

We recommend ICER abandon use of its EBM rating matrix when assessing treatments under the modified Framework. Because ICER will not incorporate functional changes to account for the inherent uncertainty surrounding clinical evidence for treatments with very small patient populations (or for treatments that have not yet been or only recently approved by the FDA), we are concerned that any evidence-rating under the existing EBM would inappropriately find the body of available evidence "inconclusive" – confusing stakeholders about the value of these treatments and potentially limiting patient access. We do not believe that a qualitative discussion of these issues is sufficient to negate any prominent display that, according to the ICER-developed EBM, there is inconclusive evidence for a particular treatment.

Sections 3.1–3.4 – Willingness-to-pay and value-based pricing benchmark adjustments

Standard cost-effectiveness models would be produced for treatments under the modified Framework. However, reports would acknowledge the uncertainty in translating patient outcomes into QALYs for ultra-rare conditions. The proposed revision would widen ICER's willingness-to-pay threshold to $50,000 - $500,000 per QALY, with no special weighting for individual conditions. Value-based price benchmarks would continue to use the standard range of $50,000 - $150,000 per QALY, but the reports will note that stakeholders often give special weighting or other considerations for medicines that treat ultra-rare diseases that lead to higher-

[4] As just one example, under the EPSDT standard, if there are no other services that are comparable in terms of safety and effectiveness, then the service at issue is likely to be found medically necessary, and thus, must be covered for Medicaid-eligible children. See Centers for Medicare & Medicaid Services, EPSDT – A Guide for States: Coverage in the Medicaid Benefit for Children and Adolescents, at 10 (2014), *available at* https://www.medicaid.gov/medicaid/benefits/downloads/epsdt_coverage_guide.pdf.

cost effectiveness ratios. When ICER cannot translate relevant inputs into QALY measurement, it proposes to cross-walk available data to a cost-consequence price.

Notwithstanding our objections to the use of QALYs described above, we support the broadening of the willingness-to-pay threshold. We recommend ICER also expand its value-based pricing benchmark for these treatments to reflect their long-term value.

Traditional incremental cost-effectiveness ratios are inherently higher for treatments that will be administered (or whose benefits accrue) over very long time horizons. Not broadening the value-based pricing benchmark in conjunction with the broadening of the willingness-to-pay threshold for these treatments penalizes medicines that treat or cure diseases that would otherwise impact an individual for his/her entire life.

We believe that ICER should strongly and clearly characterize the inherent uncertainty in developing cost per QALY metrics for ultra-rare diseases. Much smaller patient populations than those for traditional therapies introduce greater variability across a range of metrics. ICER should be prepared to describe in detail how a "high" cost per QALY measurement could be due to the uncertainty in dealing with small populations. We note that many of these considerations also exist when assessing the value of innovative medicines for serious diseases with patient populations greater than 10,000.

We also have numerous concerns about the process by which ICER would conduct its reviews when QALYs cannot be derived from patient outcomes measures. Substituting data from one indication to another – with no apparent checks or independent assessment of their appropriateness as a proxy – risks undermining ICER's fundamental approach to value assessment. These types of substitutions can also suppress the nuance and uniqueness of the patient voice. ICER should avoid creating ad hoc methodologies to make the assessment of a new treatment feasible. **We recommend ICER categorize and prominently note that assessments conducted under this process are "incomplete."**

Section 4.1 – "Other benefits and disadvantages" and "contextual considerations"

Consistent with its recent changes to the standard Value Framework, ICER would work with stakeholders to incorporate "other benefits and disadvantages" and "contextual considerations" into these assessments.

BIO supports the inclusion of a broad range of societal impacts when assessing the value of all medicines – not just those that treat ultra-rare diseases. We encourage ICER to work collaboratively with patients living with these conditions and the clinicians treating them to understand the full range of impacts that treatments for potentially debilitating conditions can bring. As ICER alludes, treatments for ultra-rare diseases require even more context and consideration of societal effects as the treatment being assessed is often times the first in its class.

While we support ICER's proposal to explore and include these factors in its assessment of these treatments, we request the Institute provide additional clarification around how these

benefits will functionally impact ICER's reports. As we commented in the revisions to the standard Value Framework, these factors must not only be investigated and described in the assessment, but meaningfully impact its outputs. Specifically, it is unclear whether ICER will utilize these considerations in its assessment of "value for money." We understand the difficulty in incorporating non-quantifiable or other metrics that fall outside the traditional dimensions of cost-effectiveness analysis. But we encourage ICER to work with stakeholders to the greatest extent possible to ensure these other considerations are incorporated into its assessments and conveyed to stakeholders in a meaningful way.

As part of this engagement, we urge ICER to place patient and caregiver engagement at the center of its assessments. Whether in the context of QALYs or other measures, ICER's goal should be a better understanding of the outcomes that are relevant and meaningful to patients. In addition, meaningful endpoints specific to patients and their disease state, such as alleviation of symptoms or the ability to be productive in work or home settings, may not be reflected by global or specific clinical measures that feed into a QALY – effectively reducing the validity of the Framework in assessing value on patient-centric outcomes.

We also encourage ICER to engage patients and caregivers at the start of its process, to inform its initial draft scoping document, and throughout its evidence collection and analysis process. The Institute should maintain transparency with respect to its incorporation of stakeholder input. At a minimum, we urge ICER to ensure that as part of each assessment, it describe how patient input and preferences were considered and incorporated. This will help facilitate accountability between ICER and the patients who will be impacted by its activities.

Section 5.1 – Research and development costs for new treatments for ultra-rare conditions

ICER proposes to develop a template for manufacturers to provide information on the "research, development and other relevant costs related to new treatments for serious ultra-rare conditions" that would be included in future ICER reports.

We strongly object to ICER attempting to collect this information from manufacturers and recommend the Institute halt its efforts to develop methods to incorporate it into future reports. As a private third-party entity, ICER does not have the authority to seek or publish this type of competitively sensitive information. The organization also lacks sufficient safeguards to ensure any information given to ICER would remain confidential.

Attempting to collect relevant research and development costs for any one therapy also presents significant operational hurdles that vastly outweigh supposed benefits of its disclosure to ICER. Many manufacturers develop multiple product lines simultaneously, with a discovery in one area informing investment in another. In the pre-clinical phase, a company may make broad-based investments that have significant impact over time but are not linked to any one product in particular. Prices for approved medicines must also account for the research and development of those products that are investigated but ultimately fail. Finally, mergers and acquisitions, licensing, and joint development arrangements would greatly impede the development of any common template that could be used across different products. Isolating the research and

development costs for any one product would therefore be extremely difficult – if not impossible.

Section 6.1 – "Long term value for money" designation

Votes on a medicine's "long-term value for money" would still be conducted under the base case of $50,000 - $175,000 per QALY, but medicines falling above this price threshold would no longer receive a designation of "low" long term value.

BIO agrees that medicines assessed under this modified framework should not be designated as "low value." Rather than operating under the arbitrary constraint of $50,000 - $175,000 when determining long term value for money, we recommend ICER deliberate solely on the contextual consideration and other benefits and disadvantages when assigning this designation, given that there are many other equally valid considerations.

Conclusion

BIO appreciates the opportunity to submit our feedback on ICER's revisions to its Framework for treatments for ultra-rare diseases. We hope this continued dialogue will help to produce tools for value assessment that recognize value's dynamic nature and fully incorporate the nuance and complexity of issues surrounding treatments for rare disease. Please feel free to contact me at (202) 962-9200 if you have any questions about these comments or if we can be of further assistance.

Sincerely,

/s/

Alex Keeton
Director
Policy Research & Analytics

Genentech
A Member of the Roche Group

September 25, 2017

Steven D. Pearson, M.D., M.Sc. FRCP
President
Institute for Clinical and Economic Review
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Boston, MA 02109

RE: Recommendations for Enhancing the Proposed adaptation of the ICER (Institute for Clinical and Economic Review) value framework for the assessment of treatments for ultra-rare conditions

Submitted electronically via: publiccomments@icer-review.org

Dear Dr. Pearson:

Genentech, a Member of the Roche Group (Genentech) is dedicated to bringing best-in-class therapies to patients within areas of high unmet need and recognize the need in making the health care system more effective and efficient for all stakeholders involved. Therefore, we are actively engaging and responding to ICER's national call for stakeholder feedback and have addressed in this letter the ICER priority areas of consideration in its **proposed adaptation of the value framework for the assessment of treatments for ultra-rare conditions** to improve the credibility and relevance of the ICER reviews. We implore ICER to consider the recommended adjustments keeping in mind that for a patient with an ultra-rare disease, the choice of and access to impactful and life-saving treatments is of paramount importance.

In addition to our comments on the priority areas outlined by ICER, we would like to take this opportunity to provide feedback on more general aspects of the ICER processes.

First, Genentech respectfully asks ICER to fully disclose all data sources and approaches that inform the contextual considerations sections of ICER reviews, to provide increased transparency into the assessment process.

Second, and as suggested throughout this letter, we recommend the routine use of sensitivity analyses in modeling to explore heterogeneity of treatment effects and avoid an over-reliance on methods based on averaged estimates. The accuracy of these analyses would bolster the assumptions of models with such sensitivity analyses.

Third, as ICER continues to refine its overall communication process, we recommend ICER extend the review times for stakeholders to provide comments in order to increase the level and quality of stakeholder engagement.

Finally, we recommend that ICER clearly communicate to the media/in press releases the interim nature of the Draft Review Report, so that no premature conclusions are made during this period.

A. Response for the six areas solicited by ICER:

1.1 ICER will consider using an adapted approach to value assessment for treatments that will be called a "potential major advance for a serious ultra-rare condition" if the three following criteria apply:

- **The treatment is envisaged for a patient population of fewer than 10,000 individuals**
- **There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals**
- **The treatment offers a major gain in improved quality of life and/or length of life**

1.2 ICER will include in its initial draft scoping document a recommendation on whether a treatment meets the above criteria. Following formal public comment, ICER will make a final decision on whether the treatment meets these criteria and will therefore be appraised using an adapted approach.

We recommend that ICER add more clarity to the basis for the 3 thresholds described in section 1.1. Establishing artificial criteria for number of patients potentially treated or trying to specify a different threshold of uncertainty for treatments of ultra-rare conditions would be more likely to obscure important distinctions related to these treatments than to aid in consistency and transparency of decision-making. Treatments should be evaluated for individual disease areas independent of potential for future development in other areas and the assessment of whether treatments offer a "major gain" should be clearly defined. Furthermore, ICER should involve clinicians who are knowledgeable experts in the ultra-rare disease area under review, consistently throughout the entire process, including the scoping phase of the assessment. The documented inclusion of such expert review will ensure accurate information about each disease area and specific challenges that patients face, are incorporated into reviews to make ICER's recommendations more comprehensive.

2.1 For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultra-rare conditions against historical controls will be highlighted.

Section 2.1:
The statement "*... The commonly used approach of evaluating major advances for severe ultra-rare conditions against historical controls will be highlighted.*" is unclear. We recommend that the evaluation be conducted against historical controls in the same disease area, pending available data, rather than looking for surrogate or comparative disease areas,

so that these differences can be highlighted using qualitative methods. We urge ICER to clarify this point.

3.1 For assessment of cost-effectiveness of a potential major advance for a serious ultra-rare condition, ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.

3.2 For these treatments ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from $50,000 per QALY to $500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.

We recommend that ICER consider the well documented methodological concerns associated with using a QALY, in particular in the area of rare diseases. QALYs are heavily weighted by instruments used to derive preference and developed with popoulation averages, both areas of very limited information in rare diseases. The use of QALYs to assess value of treatments in rare diseases raises many concerns around the ability to accurately characterize the value that patients and their families truly derive.[1] An alternate approach may be including a Cost-Effectiveness Acceptability Curve (results of the probability of Cost-Effectiveness at different willingess to pay thresholds.) This approach enables stakeholders to interpret results along a range of values. Furthermore, given the challenges associated with developing a cost-effectiveness model for a rare disease in terms of identifying data, determining outcomes and considering comparators, we implore ICER to consider whether this is the best approach to assess treatments for rare diseases.

3.3 ICER will calculate a value-based price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

3.4 When ICER 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. Instead, ICER will provide a crosswalk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found.

As previously stated, we urge ICER to consider whether calculation of a value-based price is appropriate given the aforementioned challenges of assessing treatments for rare diseases. If, in fact, ICER deems the value-based price benchmark is needed within the modified framework, it would make sense to widen the standard range up to the same amount to

[1] Measuring Value in Medicine: Uses and Misuses of the QALY. Partnership to Improve Patient Care. June 2017. Available at: http://www.pipcpatients.org/resources/white-paper-uses-and-misuses-of-the-qaly-ethical-issues-and-alternative-measures-of-value

$500,000 per QALY. We recommend that ICER clarify the "special weighting" that may be applied to inform potential *"coverage and funding decisions at higher prices."*

4.1 For report sections on "other benefits and disadvantages" and "contextual considerations," ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

We applaud that *"ICER reports will seek input from patients and clinical experts on the potential impact of a new treatment on the entire "infrastructure" of care…"*
We do recommend that ICER further characterize the type of additional benefits (and presumably broader costs) ICER will include and how these should be measured. Inclusion of indirect costs from the perspectives of both patients as well as caregivers are critical components of these costs and should be explicitly called out. This includes areas such as impact on patients' and caregivers' productivity, burden on and costs of caregiver support, as well as often underreported mental health challenges. With that, we suggest that these broader attributes be incorporated, beyond contextual considerations, into analyses that inform a QALY measure elicited from the patient and caregiver.

5.1 ICER will conduct over the coming year a collaborative process through which it will seek to develop a template for providing information in its reports on the research, development, and other relevant costs related to new treatments for serious ultra-rare conditions. Until this template is completed, ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.

In our view, it would be extremely difficult to provide ICER with accurate R & D costs at a "per-molecule level." With regard to quantifying drug development costs, there is no credible way to characterize the research and development costs of a molecule, since the launch of a molecule is based on years of cumulative research, and often multiple research and development programs, including some that failed. In addition, there are multiple factors that complicate the ability to ascertain drug development costs for a single molecule including, but not limited to, the following: mergers, acquisitions, and joint development programs.

Further, while R & D costs represent one consideration in the drug pricing decision process, such pricing decisions are multifaceted and complex; they requiring multiple inputs and a range of perspectives. Genentech aims to price products responsibly by taking into consideration the benefit our products deliver to patients and their families, as well as the company's mission to improve the lives of patients with serious or life-threatening conditions – both in terms of patient access today, and in our commitment to discovering and developing breakthrough medicines for patients of tomorrow.

As we understand it, ICER's mission is to help provide, as an independent source, an analysis of evidence on effectiveness and value to improve the quality of care for patients. A particular drug's direct R&D costs are wholly unrelated to these assessments. Indeed, linking prices to R&D costs undermines the whole process of value assessment, by contending that prices of innovative products should be set on the basis of industry costs, instead of on

benefits to patients. This is inconsistent with the principles of health economics, and also appears to be inconsistent with ICER's stated mission.

6.1 During public meetings of ICER's independent appraisal committees, votes on the "long-term value for money" of treatments for serious ultra-rare conditions will be done according to the same procedures for other interventions, i.e. if the base case estimate falls between $50,000-$175,000 per QALY. However, for treatments of ultra-rare conditions, ICER will not assign any designation of value if the base case cost-effectiveness ratio is above $175,000 per QALY.

We recommend that ICER consider what informs this long-term assessment of value given that treatments for rare-diseases may have ICERs outside of the $50,000 to 175,000 per QALY range used in the overall assessment framework. Given the earlier discussion on the limitations of QALYs in this area and the importance of incorporating other data such as indirect costs, the purpose of assessing long term value based on a cost per QALY threshold seems unclear in terms of how this could facilitate decisions for access to treatments.

B. Additional areas of consideration:

While we applaud ICER's inclusion of patients' input, there remains a gap for patient involvement directly in the assessment for each review as discussions seem to be primarily focused on cost containment. We, therefore, recommend that ICER include patients with the actual disease and caregivers on the panel of each review to provide robust perspectives on the impact of rare disease on patients, caregivers and society at large. Areas to further assess include impact to daily functioning, impact on productivity & employment as well as burden on caregivers.

With regard to "contextual considerations", ICER should quantify benefits such as savings in indirect costs (e.g., caregiver burden, productivity) by including these benefits in the cost-effectiveness analysis as sensitivity analyses. Work productivity, for example, can be quantified and incorporated into the economic value equation. A notable example is quantification of productivity loss using the Work Productivity and Activity Impairment (WPAI) Questionnaire in the assessment of absenteeism, presenteeism, and daily activity impairment due to general health or due to a specific health condition; it has been widely used and validated in many diseases[2].

In terms of cost-effectiveness analyses, the measure of quality-adjusted life years (QALY) systematically undervalues treatments addressing the needs of older patients (favoring interventions in youth over those targeted by older populations), and treatments for fatal illnesses, such as cancer (by undervaluing survival benefits in patients presumed to have poor quality of life). As noted by Whitehead and Ali, there are an increasing number of debates about QALY, for example: (1) is a QALY the same regardless of age, disease severity, sex, social role, region of residence, etc.; (2) should the value of health come directly from patients or the general population as in the case with QALY? The latter is problematic since

[2] Available at: http://www.reillyassociates.net/Index.html

quality of life improvements provided by new treatments may be valued less by the general population but valued higher by individual patients suffering from the condition.[3] Thus, the use of dollar-per-QALY thresholds potentially shortchanges the impact of innovative medicines on individual patients and in turn, undermines efforts to support personalized medicine.

Since there is no appropriate or universally accepted threshold in the US, we recommend not anchoring to an explicit threshold, but rather presenting the analysis and sensitivity analysis using a range of thresholds for more flexible and adaptive decision-making. It is important to note the challenges and limitations of applying a one-size-fits-all dollar-per-QALY threshold, in particular for rare diseases. Neumann et al recommend multiple thresholds be considered, from $50,000, $100,00 and $200,000-per-QALY since "there is no threshold that is appropriate in all decision context". [4] Neumann et al also note that much more work is required to elucidate the comparative effectiveness and cost-effectiveness of existing care, thereby, recognizing the limitations of QALYs. Genentech believes measures of benefit and effectiveness can, and should, vary across evaluations, since not all diseases have the same societal impact.

In closing, Genentech appreciates the opportunity to provide comments on the proposed adaptation of the value framework for the assessment of treatments for ultra-rare conditions and we hope that these comments will contribute to building a more comprehensive framework. We are committed to being engaged with ICER to improve the overall process. We believe that increasing the transparency, systematic approach and accuracy of evaluations will allow stakeholders to better understand and comment on the value framework assessments. Importantly, we urge ICER to consider the patient ecosystem in its assessment as to not hinder access to new and innovative medicines to patients in these diseases that carry the greatest unmet needs for patients and their families.

Kind Regards,

Jan Hansen, Ph.D.
Vice President, Evidence for Access
US Medical Affairs
Genentech, A Member of the Roche Group

[3] Available at: http://bmb.oxfordjournals.org/content/96/1/5.full.pdf

[4] Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness – the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371(9):796-7.

September 25, 2017

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

Dear Dr. Pearson,

We, members of the rare disease community, including patients with melanoma, rare liver diseases, liver-mediated diseases, and liver cancers, appreciate the opportunity to comment on the proposed adaptation of the ICER "Value Framework Assessment for Treatments That Represent a Potential Major Advance for Serious Ultra-Rare Conditions".

We are highly concerned that the premise for this exercise is as evidenced in the quote by Hughes in the conclusion, "whether . . . funding should support the provision of ultra-orphan drugs" and further " that ultra-orphan drugs are reimbursed at all" to call into question the appropriateness of developing and paying for the treatments for patients with rare conditions. For any to have confidence in any value framework developed the essential dignity of patients with rare diseases and right to a chance for optimal health equal to patients with other diseases must be affirmed. Resource allocations for health are choices, they are neither fixed nor finite, nor should they be viewed as zero sum games pitting people against each other.

Ultra-rare is an arbitrary category designation

ICER's first proposal establishes a novel category of disease: the "ultra-rare" diseases. This category is arbitrary and undermines the Orphan Drug Act of 1983 which has proven to be a successful driver of innovative, life-changing and life-saving treatments for patients in the United States. Also, under ICER's proposed amendment, patients who have a disease that affects between 10,000 and 200,000 individuals will be effectively lumped into the "common diseases" category, and the complexities of clinical trial recruitment, study design, evidence generation, and relevant elements to value calculation involving rare diseases that fall in that category will be essentially ignored.

The ICER proposed amendments do not demonstrate the practical differences between either the R&D challenges or the value of a treatment for 9,000 patients and 11, 000 patients or 21, 000 patients. The basis for the criterion of "little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals is unclear. Many factors, not the least

of which are scientific discovery accelerating in a disease state once a treatment is available, may expand use. Also, major gain is a vague term.

Use of QALYs are methodologically undersound and misrepresents value of interventions for people with disabilities and chronic diseases

ICER proposals to use QALYs make any determinations out of concordance with federal policy since by law "the Secretary [for Health and Human Services] shall not utilize such an adjusted life year (or similar measure) as a threshold to determine coverage, reimbursement, or incentive programs" in the Medicare Program.

As so well articulated in the Partnership to Improve Patient Care's white paper, "Measuring Value in Medicine: Uses and Misuses of the QALY", the disconnect in using an academic tool to influence real-life policy based on a presumed ability to quantify the quality of individual patients' lives can be seen in how QALYs are measured and calculated. Many individuals included in population-based surveys can only imagine their response to theoretical scenarios and may be unable to realistically answer how much they value their lives in a particular state of health or what they are willing to trade to treat a hypothetical health condition or symptom.

The seminal Second National Panel on Cost Effectiveness notes that the "quality and usefulness of QALYs depends on the quality and validity of the utility scores used to calculate them" (Neumann, Sanders, Russell, Siegel, & Ganiats, 2017). The methodological difficulty in measuring patient preferences becomes clear when examining the sheer number of survey instruments and methods to measure QALYs. There is no one, single accepted way to determine how to best quantify the value of a particular health state or intervention (Gafni, 1994; Ryan & Farrar, 2000).

The way in which conventional QALYs assign value to health gains from an intervention prioritizes care to individuals with a higher baseline health status, which may result in individuals with disabilities or chronic conditions being disadvantaged.

Perhaps the most concerning of all, in the eyes of a patient advocacy organization, is ICER's plan to not vote on ultra-rare treatments that exceed $175,000 cost per QALY threshold. Preemptively declaring a pricing cap without debate means that ICER will assess treatments without input from patients or caregivers. Eliminating the patient and caregiver narratives from an evaluation of treatment value takes away an opportunity for patients and caregivers to advocate for themselves and their own health. It is imperative that, in assessing the value of any treatment, especially for rare diseases, the patient and caregiver experience be heard.

Proposals would discourage innovation for patients with rare diseases

Discounting the very real practical challenges of clinical research and development in all rare diseases and sending categorical price caps for consideration will greatly reduce investment in therapies for rare diseases, a landscape that only has 625 FDA approved orphan drug approved treatments for 7,000 conditions. Adoption of these proposals could have a profound negative impact on patients with both so-called "ultra-rare" and rare conditions such as, autoimmune hepatitis, primary sclerosing cholangitis primary biliary cholangitis (PBC) and fibrolamellar cancer, rare hepato-biliary diseases which require more, not fewer, incentives for research as they have no cures.

In conclusion, we ask that ICER assess what it means to be the patient or the caregiver of a loved one with a rare disease. Facing barriers to diagnosis, support, research, treatment, and coverage for a variety of interventions and services, they do not need additional disadvantages. Rare disease patients, whether their disease affects 200 or 200,000, deserve equal and fair access to a market that promotes innovation. Patients deserve the chance to advocate for themselves, and caregivers deserve their narratives to be heard. We strongly urge ICER to reevaluate the proposed amendments to the Value Framework Assessment of Treatments for Ultra-Rare Conditions.

Sincerely,

Global Liver Institute

Fibrolamellar Cancer Foundation

Melanoma Research Foundation

Patients Rising

September 25, 2017

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

Submitted Electronically: publiccomments@icer-review.org

RE: Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions

Dear Dr. Pearson,

Over the past several years, increasing attention has been drawn to orphan drugs and their associated costs, with particular focus on the potential for manufacturers to navigate orphan pathways to "blockbuster" sales and revenue. The undersigned organizations represent diverse stakeholders, including life sciences companies and patient advocacy organizations, with a shared commitment to developing and ensuring access to treatments for the subset of rare disorders that impact extremely small patient populations. Our concern that reactive health policies designed to combat perceived orphan drug "gaming" would have an unintended and disproportionate impact on ultra-rare diseases was one of the driving forces toward our collective voice. We believe that ICER's initiative will have a bottom-line impact on whether or not some patients with ultra-rare diseases will have access to a treatment option.

ICER's decision to draft an adapted framework for evaluating treatments for ultra-rare conditions was a well-intentioned demonstration of its recognition that there are unique concerns and challenges in developing treatments for extremely small populations. We appreciate the opportunity to offer our comments to ICER's proposed framework adaptation. We provide a brief introductory summary of the ultra-rare disease stakeholder perspective on the challenges patients, caregivers, and innovators face. Our comments reflect our overriding commitment to preserve, and build upon, the innovation-driving environment envisioned when President Reagan signed the Orphan Drug Act of 1983 (ODA), and are grouped to express our concerns with:

- The foundational assumptions and policy goals driving ICER's framework;
- ICER's criteria for determining whether a treatment for an ultra-rare condition should be evaluated within the adapted framework; and

- The potential inappropriateness (and inherent associated difficulties) with making a value judgment intended to drive decisions to grant or deny access to the only FDA-approved treatment for a serious, ultra-rare condition.

We also make specific recommendations to guide ICER's framework and patient engagement strategy in instances, such as diseases with multiple, comparable FDA-approved therapies, where a value assessment for an ultra-rare disease treatment may be of value:

- ICER should incorporate long-term patient benefit into its assessment to accurately capture the value to patients and their families;
- ICER's grafting of Quality Adjusted Life Year (QALY) metrics and a willingness to pay threshold onto evaluations of ultra-rare disease treatments will complicate research and development, and encourage payer denial of necessary medical care;
- ICER should proactively and exponentially increase its engagement with the patient and caregiver community throughout its process; and
- ICER should not directly or implicitly require innovators to provide it with information that is not otherwise publicly available, and not relevant to safety or efficacy.

Background

Congress drafted the Orphan Drug Act's (ODA's) incentive framework to counter the commercial realities associated with research and development toward treatments for serious medical conditions affecting small populations. During the ten years preceding the ODA, just 10 rare disease products had obtained FDA approval; since the ODA's implementation, over 600 rare disease drugs and biologics have been developed. Countless lives have been improved, or saved by new therapies spurred by the ODA, however, millions of Americans affected by a rare disease are still waiting and hoping for treatment or a cure:

- 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.

While the ODA clearly boosted interest in pursuing rare disease treatments, its incentives are a fixed set of counterbalances to the economic calculation of research and development costs, projected risk, and population-based revenue estimates. Reimbursement mechanisms and hurdles can tip the scales for or against pursuing a specific drug candidate for an orphan indication. For patient populations approaching the 200,000 orphan disease limit, the ODA incentives may be sufficiently robust to mitigate clinical trial and reimbursement risks. As affected populations

dwindle below 20,000 or even into and below the hundreds, however, the balance is far more fragile.

We support and expect to participate in continuing dialogue among all stakeholders to expand equitable access to quality health care. We are, however, concerned that ICER's efforts to recognize the unique challenges associated with ultra-rare diseases may function only to impede access and inject sufficient uncertainty to chill future innovation. This concern is grounded in evidence -- researchers observe that price thresholds would slow drug innovation by 23-32 percent with as much as a 60 percent reduction in Research and Development (R&D) early stage projects.[1][2]

Foundational assumptions and policy goals driving ICER's framework

In its concluding paragraphs to the proposed framework adaptation, ICER discussed its guiding principle of attempting to balance competing ethical interpretations of "fairness" in the context of healthcare spending on costly treatments for ultra-rare conditions. Noting the ethics driving reimbursement for high-cost ultra-rare conditions, ICER opined that the balance was well-captured by *Hughes, et al.*, -- "[t]he consequence, however, is that the opportunity cost of supporting the use of ultra-orphan drugs necessitates that patients with a more common disease, for which a cost-effective treatment is available, are denied treatment."[3]

The undersigned stakeholders include patients with serious ultra-rare disorders, their caregivers, and those who have experienced the life-changing loss of a loved one to a disease for which no treatment exists. Industry signers know what it means to look into the eyes of a parent with the shared hope that a new technology might offer a step closer to a long and fulfilling life for their child. Hughes' world-view, if operationalized and implemented to drive treatment and reimbursement decisions, paints a dark future for individuals with ultra-rare diseases and their families.

A recent study examining the relationship between disease rarity and treatment cost found, not surprisingly, that the cost of orphan drugs in European markets is inversely proportional to disease prevalence.[4] If it were true that one person accessing their only available treatment might decrease access to several patients with more common conditions (and we do not believe this is an established fact), the "fairness" calculus would always deny treatment to the patient with the ultra-rare disorder simply by virtue of utilitarian principles.

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[1] Vernon A, "Examining the link between price regulation and pharmaceutical R&D investment ." *Health Economics*. 2005. 14: 1-16.

[2] Kutyavina M. "The effect of price control threats on pharmaceutical R&D investments." (2010).

[3] Hughes DA, Tunnage B, Yeo ST. Drugs for exceptionally rare diseases: do they deserve special status for funding? QJM : monthly journal of the Association of Physicians. 2005;98(11):829-836.

[4] Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5405566/pdf/zjma-5-1299665.pdf

We also note that ICER declined to develop a framework for ultra-rare disease treatments that would have a distinctly appropriate structure and evidentiary standard, stating that "[i]nstead, the goal is that ICER reports be able to provide specific context and additional information so that decision-makers will be adequately informed of the distinctive character of the evidence and the broader considerations **that should be part of policy decisions** regarding treatments for rare conditions." (emphasis added) 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 "policy decisions" that have already been enacted into law for Medicare, Medicaid, and Affordable Care Act issuers, as well as the contractual arrangements between parties to employer-sponsored healthcare coverage. The US healthcare system 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 extremely rare with one, costly, available treatment.

Rather than applying the concept of vertical equity in healthcare to assessing value of ultra-rare disease treatments, we urge ICER to follow the lead of clinical and health economic experts such as those convened in conjunction with the Annual European ISPOR Congress in Berlin, Germany, in November 2012. In discussing whether and how to quantify the relative cost and "value" of ultra-rare disease treatments, the expert consensus statement noted:

> As to the health economic evaluation of interventions for URDs, the currently prevailing logic of cost-effectiveness (using benchmarks for the maximum allowable incremental cost per quality-adjusted life year gained) was considered deficient as it does not capture well-established social preferences regarding health care resource allocation.[5]

A published cost-effectiveness assessment for enzyme replacement therapy for Gaucher's disease grappled with the inherent tension of monetizing the relative value of a life-saving therapy for an ultra-rare disease. The authors questioned the utility of their inquiry into the incremental cost effectiveness of ERT:

> It is highly improbable that, whatever the findings of such research, the ICER could be brought down by the orders of magnitude required to make ERT an efficient use of health service resources. (The possible exception to this would be investigating the most efficient alternative treatment strategies for using ERT in a paediatric population only.) Moreover, if under equity considerations for orphan diseases the NHS feels it is important to provide this drug, regardless of its cost-effectiveness, then refining the precision of the ICER estimate also becomes superfluous.[6]

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[5] Schlander, et al., *Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement*, J Mark Access Health Policy. 2016 Oct 27;4.

[6] Connock, et al., *The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review,* Health Technol Assess. 2006 Jul;10(24):iii-iv, ix-136.

As more fully detailed below, we ask that ICER refrain from normalizing any cost-based denial of healthcare to these vulnerable patients under the guise of evidence-based, objective, or rational allocation of finite resources.

ICER's criteria for determining whether a treatment for an ultra-rare condition should be evaluated within the adapted framework

To "qualify" for a distinctive assessment approach, ICER proposes that a treatment must be expected to affect a patient population of fewer than 10,000 individuals, with little chance of future expansion of indication or population to above 20K, and it must offer a major gain in quality and/or length of life for patients with a serious condition. ICER opined that:

> Only when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation.[7]

ICER's conclusion that "only" patient populations below 10,000 warrant special consideration provides no context or basis.

- We recommend ICER raise the threshold and explain the basis of its patient-threshold determination. The inverse relationship between disease prevalence and treatment cost supports a more fluid approach;

- The idea that treatments for ultra-rare diseases with near-term (or even concurrent) market potential for non-orphan populations are different from pure ultra-orphan products has some validity. Operationalizing the concept to an assessment that a product has "little chance of expansion" appears to create uncertainty and inject a subjective and speculative component. For example:

    - Is there a presumption of broader utility that must be negated?

    - How "little chance of expansion" determined? Clinical trials in progress? Emerging off-label use? Or is it a more tangential determination relying on shared disease processes and/or scientific speculation?

We urge ICER to keep its inquiry in the near-term, and adhere to its evidentiary standards in assessing "future expansion" rather than engage in speculation. We also disagree with ICER's assessment that potential future expansion beyond 20,000 patients places a treatment in the same category as a potential blockbuster. It is quite possible that a treatment option developed for one

[7] https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf, at p. 3 of 9.

ultra-rare condition could be effective for other ultra-rare or orphan conditions. Follow-on indications require innovator investment, could take years to gain approval, and may not come to fruition at all. Moreover, the possibility that a treatment developed for an ultra-rare disease could eventually be more broadly used to enhance the lives of a broader population does not undercut its value – it underscores the potential public benefit of scientific inquiry.

Potential inappropriateness, and inherent associated difficulties, with making a value judgment intended to drive decisions to grant or deny access to the only FDA-approved treatment for a serious, ultra-rare condition

As detailed more fully above, we are concerned that any value assessment of a treatment for an ultra-rare disorder for which no FDA-approved treatment alternative exists would be of limited use to payers due to statutory and/or contractual limitations. We also note that ICER identified a number of instances in which it would be unable to apply its framework. The majority of treatments representing the only available option for an ultra-rare disease would likely fall within these circumstances.

First, ICER notes 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." Instead, ICER will provide a crosswalk to a treatment and condition pair that is the closest clinical analogue that ICER can identify.[8] We are unable to envision any situation under which a treatment for a previously untreatable ultra-rare condition should be judged based upon "the closest" surrogate disease state and treatment, and suggest that ICER simply refrain from conducting an assessment that it cannot complete with scientific credibility.

Similarly, ICER notes that "other methodological changes will be made when special circumstances make it extremely difficult to estimate the impact of treatment on quality-adjusted life years, such as when diseases affect very young children or are associated with pronounced mental and/or physical disability in patients of any age." We agree with ICER that such situations likely will exist, and may even predominate, and appreciate its recognition that the QALY methodology is a poor fit.

Although ICER has suggested that in situations where no treatment has been available in the past, it will seek input from patients and clinical experts on the potential impact of a new treatment on the entire "infrastructure" of care, we do not believe this type of "sidebar" consideration cures ICER's inability to apply its standards and arrive at fair, ethical, and reasonable conclusions. An assessment purporting to be evidence-based that requires *ad hoc* methodological changes, relies on surrogate disease states, and/or contains disclaimers related to various unmeasured patient and societal considerations strays far beyond the purpose and scope

[8] https://icer-review.org/wp-content/uploads/2017/05/ICER_Proposed_VAF_Adaptations_Orphan_Drugs_072517.pdf, at p. 5 of 9

of ICER's core functions in the overall healthcare system. Again, we urge ICER to maintain transparency and scientific integrity, and expend its resources where they can be of greatest value, i.e., in determining the value of a treatment within a subset of available options.

Specific recommendations to guide ICER's framework and patient engagement strategy in instances where a value assessment for an ultra-rare disease treatment is potentially appropriate

We agree that the challenges to developing and marketing products for ultra-rare diseases warrant a different approach to assessing value than treatments for commonly-occurring disease states. 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 address ultra-rare diseases are unlikely to result in meaningful differences in ICER's assessment or how its assessments are interpreted.

ICER should incorporate long-term patient benefit into its assessment to accurately capture the value to patients and their families.

ICER proposes to retain its generally-applicable standard of evidence when assessing ultra-orphan products, even as it acknowledges that low patient populations may make traditional RCTs impracticable and statistical analyses complicated. A "uniform" approach, particularly one that is substantially the same as the approach used for treatments in large patient populations, will most likely fail to yield meaningful information on specific ultra-rare disease treatment. It will, however, inject additional risk and uncertainty to innovators considering the fiscal prudence of investing in ultra-rare disease therapies.

This is particularly true if the long-term benefits are not sufficiently captured to offset budget impact and provide a more accurate, holistic picture. In evaluating alternative treatment options for ultra-rare disorders, we urge ICER to acknowledge through its value assessment process that the measure of value to patients inherently extends beyond the short-term perspective that payers often adopt. This is particularly true for ultra-rare disorders, most of which are genetic and chronic. Emphasizing the short-term budget impact of treatments using assumptions and arbitrary thresholds may be used as a rationale to restrict patient access.

ICER's grafting of Quality Adjusted Life Year (QALY) metrics and a willingness to pay threshold onto evaluations of ultra-rare disease treatments will complicate research and development, and encourage payer denial of necessary medical care.

ICER continues to rely on Quality Adjusted Life Year (QALY) as its value metric, just as with all the other treatments (including blockbuster treatments) it reviews. QALY's suffer significant shortfalls if applied to orphan disease including (1) inability to address the heterogeneity in treatment options; (2) limitations in very young or very old populations; and (3) Caregiver

QoL/QALYs usually are not considered despite the particularly profound caregiver in the context of ultra-rare disorders.

A comprehensive study on the use of incremental cost per QALY gained in ultra-rare disorder 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. Similarly, we are concerned that the willingness to pay framework will serve to impede or delay access to needed treatments. Experience in countries with technology assessment approaches that use rigid willingness to pay criteria experience less and delayed access to treatment options, and lower associated survival rates.

- ***ICER should proactively and exponentially increase its current engagement with the patient and caregiver community throughout its process***; and

We urge ICER to place patient and caregiver engagement at the center of its assessments. Whether in the context of QALYs or other measures, ICER should aim to gain a better understanding of the outcomes that are relevant and meaningful to patients. In addition, meaningful endpoints specific to patients and their disease state, such as alleviation of symptoms or the ability to be productive in work or home settings, may not be reflected by global or specific clinical measures that feed into a QALY – this reduces the validity of the framework in assessing value on patient-centric outcomes.

ICER discusses outreach to patients and patient groups as part of its inquiry. Unfortunately, this outreach does not start until the process is well underway, with ICER drafting a scoping document and permitting a 3-week time period for public comments. Patient and caregiver stakeholders should be brought into the process to inform the scoping document and identify outcomes that are of substantial importance. Similarly, the 3-week time allotment to become aware of ICER's activity, review and digest its potential impact, and organize toward meaningful comments and a continuing dialogue is far too short if ICER hopes to have patient perspectives inform the resulting analysis.

We also encourage ICER to maintain transparency with respect to its incorporation of stakeholder input. At a minimum, we urge ICER to ensure that as part of each assessment, it describe how patient input and preferences were considered and incorporated. This will help facilitate accountability between ICER and the patients who will be impacted by its activities, particularly if ICER makes its rationale publicly available. Understanding why certain patient considerations were included and others were not will greatly further the collaborative design ICER seeks to encourage.

ICER should not directly or implicitly require innovators to provide it with information that is not otherwise publicly available, and not relevant to safety or efficacy.

ICER discusses its interest in collecting information on manufacturer development costs, including how it might develop a template. "ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of

development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing." We are concerned that this level of inquiry is outside the scope of industry standards for manufacturers providing information to FDA, CMS, and private payers, and may be an unprecedented "reach" by a private entity, particularly considering ICER's implied goal of broad public disclosure. Our concerns include:

- Intellectual property issues and considerations severely compromise the ability and/or advisability of making these disclosures;
- It is unreasonable for ICER to implement value assessment methodologies that seek or demand confidential industry information;
- Standardizing this inquiry or information request sets up the possibility that ICER would incorporate an adverse inference or otherwise "penalize" rare disease treatments if manufacturers do not cooperate with ICER's disclosure requests.

We urge ICER to eliminate the disclosure proposal and template development from any final framework it develops.

Once again, we appreciate the opportunity to comment on the proposed framework adaptation. As the voice of ultra-rare disease stakeholders, we look forward to working with you in the future to facilitate patient and caregiver engagement, and to further inform your 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.

Choroideremia RESEARCH FOUNDATION

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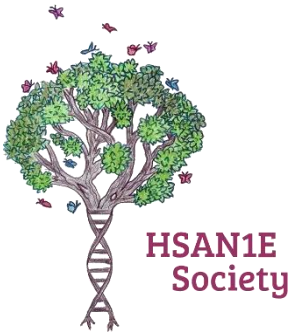

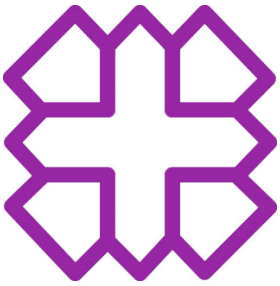

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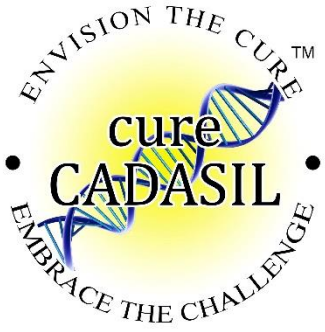

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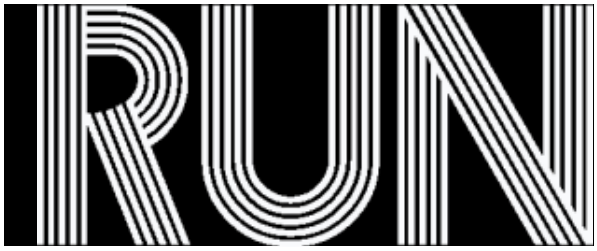


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Hannah's
HOPE FUND

Mallinckrodt Pharmaceuticals

VIA EMAIL: publiccomments@icer-review.org

September 25, 2017

Institute for Clinical and Economic Review

RE: Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions, July 2017

Dear Sir/Madam:

Mallinckrodt Pharmaceuticals ("Mallinckrodt" or the "Company") appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER)'s "Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions," (the "proposed framework"), released in July 2017.

Mallinckrodt is a global business that develops, manufactures, markets and distributes specialty pharmaceutical products and therapies. Areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; and analgesics and hemostasis products. The company's core strengths include the acquisition and management of highly regulated raw materials and specialized chemistry, formulation and manufacturing capabilities. The company's Specialty Brands segment includes branded medicines and its Specialty Generics segment includes specialty generic drugs, active pharmaceutical ingredients and external manufacturing. Mallinckrodt is engaged in the development of products to treat orphan diseases, which are defined as those impacting less than 200,000 persons in the United States under the Orphan Drug Act (ODA).[1]

The importance of fostering innovation into researching and developing new treatments for unmet medical needs, including orphan diseases or conditions, cannot be understated. An estimated 7,000 rare diseases have been identified, impacting approximately 25-30 million Americans.[2] The passage of the ODA has done much to spur innovation, leading to over 600 drugs and biologic products being developed and marketed for rare diseases since 1983.[3] Yet, more must be done; unmet need in this area remains striking, and drug development remains challenging and costly.[4] In fact, 95% of rare diseases lack an FDA approved treatment or

[1] Public Law 97-414, Jan. 4, 1983, 96 Stat. 2049.
[2] https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases.
[3] https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm; Miyamoto and Kakkis, "The potential investment impact of improved access to accelerated approval on the development of treatments for low prevalence rare diseases," Orphanet Journal of Rare Diseases, 20116:49, available at: https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-6-49.
[4] FDA Commissioner Scott Gottlieb acknowledged these costs in a recent speech: "Even when we can afford to develop breakthroughs, more people will have a hard time paying for them if we can't reduce the cost of drug development, and find better ways to capture those savings. The high cost of development also reduces competition. With the high costs, it can be less viable to develop some drugs, especially if you're second or third to market. Yet we know this kind of competition lowers prices." https://www.fda.gov/NewsEvents/Speeches/ucm575400.htm.

therapy.[5] Rare diseases disproportionately impact children; approximately 50% of people affected by rare diseases are children.[6]

As awareness regarding the number of rare diseases increases, the economic impact of all rare diseases combined is not well studied; however, it is estimated to be significant.[7] As Lopez-Bastida concluded, "rare diseases often have a chronic, intensive pattern of health care use, with extended periods of morbidity and early mortality."[8] The path to diagnosis for a patient with a rare disease averages more than 7.5 years in the US, and along the way, "patients experience an average of 4 primary care physicians and 4 specialists, usually with conflicting treatment advice and disease state information."[9] Moreover, lack of insurance coverage and uncertainty regarding which procedures and treatments may be covered adds to the patient's financial burden.[10]

Prescription drugs comprise a significant part of the solution. As a proportion of total health care spending, prescription drugs represent only a small share of such spending. In fact, national health expenditure data demonstrates that drug spending has remained steady since the 1960's, and is projected to remain at approximately 6% per year between 2016-2025, which is in line with projected growth in other health care sectors.[11] And, while claims persist regarding the rising high cost of prescription drugs, according to Murray Aitken, senior vice president and executive director of the Quintiles/IMS Institute: "After a year of heated discussion about the cost and affordability of drugs, the reality is that after adjusting for population and economic growth, total spending on all medicines increased just 1.1 percent annually over the past decade."[12]

Once available, prescription drugs to treat orphan conditions can offset the significant burdens of rare diseases. Yet, beyond the direct costs of a treating a rare disease, there are a series of other costs. While the patient/caregiver impact cannot be understated or easily quantified, significant, long-term financial costs and declines in well-being among caregivers must also be taken into account.[13] In these instances, the existence of an available treatment option can create a net positive effect through not only improved health but an economic return to the economy, societal benefits, and peace of mind for patients, family members and caregivers.

As stated above, given that 95% of rare diseases have no approved FDA treatment option, continued innovation into new and cutting-edge treatments for patients with rare diseases is

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[5] http://rareaction.org/about/rare-diseases/.
[6] https://globalgenes.org/rare-diseases-facts-statistics/.
[7] Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health Policy. 2015 Jul 31;119(7):964-79.
[8] López-Bastida J1, Oliva-Moreno J. Cost of illness and economic evaluation in rare diseases. Adv Exp Med Biol. 2010;686:273-82. doi: 10.1007/978-90-481-9485-8_16.
[9] Id.
[10] Kvancz, MS, RPh, FASHP, American Journal of Pharmacy Benefits, July/August 2016, http://www.ajpb.com/journals/ajpb/2016/ajpb_julyaugust2016/the-impact-of-rare-diseases-and-drug-therapy.
[11] https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/proj2016.pdf.
[12] QuintilesIMS Institute Study: U.S. Drug Spending Growth of 4.8 Percent in 2016, May 05, 2017, available at: https://www.quintilesims.com/press-releases/quintilesims-institute-study-us-drug-spending-growth-of-48-percent-in-2016.
[13] https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf.

critical. Thus, we are concerned that ICER's proposed framework will blunt much-needed research and development in this area.

Keeping this important context in mind, Mallinckrodt is pleased to provide additional comments on selected sections of the draft assessment framework for ultra-rare products, organized by the specific section within the ICER draft framework below. We support the opportunity to provide input into ICER's deliberations on this important topic, and encourage ICER to continue public dialogue on the topic. Our specific comments are summarized briefly and discussed more fully below.

- **Inclusion of Patient and Other Perspectives in Value Frameworks.** We support ICER's efforts to include the perspectives of patients and others as contextual considerations in any proposed framework.
- **Recognition that Certain Conditions Require Adaptation of ICER's Standard Value Assessment Framework.** We support ICER's effort to adapt its value framework methodology to address orphan or rare diseases or conditions. We are concerned, however, that the narrower proposed refinement of "ultra-rare" diseases or conditions runs counter to the Orphan Drug Act and the resulting more than 30 years of orphan drug research and development.
- **Recommend Clear Definitions and Substantiation for Key Terms.** We recommend ICER provide clear definitions for key terms and phrases used in the proposed framework and provide support for the conclusions reached in the proposed framework. In several instances, we recommend ICER consider existing definitions adopted by the Food and Drug Administration (FDA).
- **QALY and Willingness to Pay Concepts Should Not Be Adopted.** Willingness to pay is highly controversial and QALY is not sufficiently flexible in our view, and thus, should not be adopted.
- **Collection of Data on Drug Development Costs Should Not Be Adopted.** The proposal to collect data on drug development costs should not be pursued. The collection of this information is potentially in violation of Securities and Exchange Commission rules, the confidential nature of the information cannot be guaranteed, and the information may be operationally impossible to collect and accurately attribute to a specific product.

ICER Framework Section #1.1: Adaptation of Value Assessment Frameworks for Ultra-Rare Products Limited to Products for Patient Populations of Less than 10,000

ICER's proposed draft framework concludes that an adapted framework for value assessments is not needed for the vast majority of "orphan" drugs as defined by the ODA, "as sufficient patient numbers are usually available for 'routine' clinical trials, and outcome measures are likely to be relatively standardized and well-documented."

Instead, ICER proposes to use an adapted value assessment framework for orphan products when: (1) the intended patient population is fewer than 10,000; (2) there is "little chance of future expansion of indication or population" beyond 20,000 patients; and (3) the treatment potentially offers a "major gain" in improved quality of life and/or length of life.

Mallinckrodt Response:

Proposed Framework Ignores Existing Statutory Definitions

Mallinckrodt is concerned with ICER's proposed adoption of a definition of "ultra-rare" as a condition impacting less than 10,000 persons, with little possibility of impacting more than 20,000 persons. The term "ultra-rare" is not defined in the ODA, and there is no statutory basis in the law to support the creation of this new category of rare diseases. Further, the proposed framework contains no explanation or discussion regarding why this limited patient impact was selected. We strongly recommend that ICER adopt the approach set out in the ODA and adopted by the FDA over the last three decades – a condition is a rare or orphan condition if it impacts less than 200,000 persons in the U.S.[14]

Proposed Framework Fails to Appreciate the Challenges of Clinical Research

ICER's conclusions that clinical trials are routine, that sufficient patient numbers exist to conduct research "for the 'majority' of orphan drugs, and that outcomes measures are "likely to be relatively standardized and well-documented" minimizes the significant challenges inherent in clinical research.

In fact, recent provisions enacted in the 21st Century Cures Act directly contradicts ICER's statement that clinical trial designs are routine, even for products with non-orphan indications. Section 3021 of the 21st Century Cures Act directs FDA to assist sponsors in incorporating complex adaptive and other novel trial designs into proposed clinical protocols and applications for new drugs and biological products in order to facilitate more efficient product development.[15] These detailed processes will take at least 18 months, if not more, to fully implement. For example, FDA must hold a public meeting 18 months after the date of enactment of the Cures Act and issue guidance on, among other things, how to use such novel trial designs, how they can help to satisfy the substantial evidence standard, and recommended analysis methodologies. FDA staff will conduct the public meeting, further develop novel clinical trial designs and approaches, and draft the required guidance.

Further, ICER's conclusion that outcomes measures are "well-documented" is also unsubstantiated in the draft framework. In reality, outcomes measures are not standardized – they can and do vary a great deal. Often, sponsors must support research into development of outcomes measures or validation of existing outcomes measures before implementation. Thus, this conclusion lacks an understanding of the challenges in conducting clinical research, particularly in the orphan disease area.

Terms Used Throughout Framework Lack Definition and Substantiation

At multiple places throughout the proposed framework, key terms and phrases could benefit from clear definitions and substantiation. As an example, the "major gain" noted in the third prong of ICER's proposed definition in Section 1.1 is undefined and highly subjective and will undoubtedly vary based on the perspective of the person or entity observing the "major gain" (e.g., provider vs. payer vs. patient). And, the second prong in the proposed definition in Section 1.1 states that there is "little chance of future expansion of indication or population"

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[14] https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/significantamendmentstothefdcact/orphandrugact/default.htm

[15] Public Law 114-255, 130 Stat. 1033.

beyond 20,000 patients; however, no definition or explanation for the subjective phrase "little chance of future expansion" is provided. The framework would benefit, in our view, from clear definitions and substantiation for the terms used and the conclusions reached, before the proposed framework is finalized.

ICER Framework Sections #3.1-3.4: ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes to quality-adjusted life year (QALY) measures. ICER will adapt its analysis to provide willingness-to-pay thresholds for a broader range, from $50,000 per QALY to $500,000 per QALY.

Mallinckrodt Response:

Quality-Adjusted Life Year ("QALY") Measures Raises Many Issues; A More Flexible Approach is Recommended

Given the limitations of QALY, we strongly encourage ICER to make the drug value assessment framework flexible to accommodate situations when reliably measuring QALY is not feasible. Although widely used by health technology assessment agencies, QALY has significant limitations including ethical considerations, methodological issues and theoretical assumptions, and context or disease specific considerations.[16] A number of limitations with the metric have also been identified, relating to time factors, utility factors and algorithm variation. Operationally, measuring quality of life or utility (one of the two components of QALY) is a challenging process as numerous direct and indirect methods exist. Some specific issues with QALY are worth noting:

- QALY cannot be derived from some of the most vulnerable populations, including very young, very old or very sick populations;
- Patients with lower QALY whose lives are extended will have higher overall cost;
- QALY inputs are based on clinical evidence which is hard to come by for small populations of orphan diseases;
- QALY cannot adequately capture comprehensive value, such as important patient, caregiver, and societal benefits;
- QALY does not holistically assess value to an individual patient;
- QALY shortchanges the impact of innovative medicines on individual patients; and
- QALY cannot address heterogeneity in treatment options.

For these reasons, we recommend that ICER adopt a more flexible framework that is not tied to QALY.

Willingness to Pay ("WTP") Thresholds Highly Controversial

Given the conceptual deficiencies and limited practical applications in the health care field, we do not support the use of WTP as part of the drug value assessment process.

[16] Pettitt DA, Raza S, Naughton B, Roscoe A, Ramakrishnan A, et al. (2016) The Limitations of QALY: A Literature Review. J Stem Cell Res Ther 6: 334; Nord E, Daniels N, Kamlet M. QALYs: some challenges. Value Health. 2009 Mar;12 Suppl 1:S10-5. doi: 10.1111/j.1524-4733.2009.

The WTP concept is highly controversial in economic literature and the internal and external validity of such a tool is still questioned, both theoretically and methodologically.[17] Although widely used over the past 20 years, the WTP concept is clearly deficient for application in the health field. A considerable number of researchers in the literature have pointed out multiple methodological issues involving willingness-to-pay estimates. For example, WTP is a variable indicator that depends on the economic and social stratum in which the survey is carried out. Another problem linked to the instruments of WTP is due to the significant information asymmetries that exist between patients and medical practice. Results from a recently published systematic literature review covering 1994-2014 clearly showed the futility of WTP.[18] Some of the negative concerns for use of WTP are noted below:

- Could negatively affect patients with orphan diseases by decreasing access and discouraging innovation into new treatments for unmet medical needs;
- Presents significant ethical issues, in that the concept only takes into consideration the individual's willingness to pay and excludes, in the vast majority of cases, the collective (social) capacity;
- Prioritizes least costly patients, rather than the sickest; and
- Runs counter to the principles under which the ODA was enacted.

Other Proposed Methodological Changes: Terms Must Be Clearly Defined and Adequately Substantiated

In discussion under items 3.1-3.4 in the proposed framework, ICER states it may make other methodological changes when, "special circumstances make it extremely difficult to estimate the impact of the treatment on quality-adjusted life years, such as when diseases affect very young children or are associated with pronounced mental and/or physical disability in patients of any age."

The terms "very young children," and "pronounced mental and/or physical disability," are undefined in the proposed framework, and we believe the inclusion of these terms without definition or further discussion leaves much unaddressed, with the potential result that patients, including children and those with mental or physical disabilities, could be negatively impacted by future ICER value assessments. We note that FDA defines related terms as follows:

- Neonates: birth up to 1 month;
- Infants: 1 month up to 2 years;
- Children: 2 years up to 12 years;
- Adolescents: 12 years to younger than 17 years.[19]

[17] Mould Quevedo JF, Contreras Hernández I, Garduño Espinosa J, Salinas Escudero G. The willingness-to-pay concept in question. Rev Saude Publica. 2009 Apr;43(2):352-8; Aizuddin et al. Methods and tools for measuring willingness to pay for healthcare: what is suitable for developing countries? BMC Public Health 2014 14(Suppl 1):O20.

[18] Nimdet K, Chaiyakunapruk N, Vichansavakul K, Ngorsuraches S. A systematic review of studies eliciting willingness-to-pay per quality-adjusted life year: does it justify CE threshold? PLoS One. 2015 Apr 9;10(4):e0122760.

[19] FDA, "Guidance for Industry and Review Staff: Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling," February 2013, available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM341394.pdf.

The framework's proposed subjectivity could also negatively impact future drug development by stifling innovation with the adoption of vague, undefined terms that are inconsistent with FDA precedent.

ICER Framework Section #4.1: Contextual Considerations

Mallinckrodt Response:
"Value" Means Many Things to Many People, and Thus, a Variety of Perspectives Must Be Taken into Account
We recommend that ICER's drug value assessment framework be expanded to take into account caregiver, provider, societal and other perspectives. When assessing the value of medicines for any condition, including those to treat ultra-rare or rare conditions, "value" is made up of many different factors from different perspectives including the patient, caregiver, provider, insurer, and society, to name a few.

Patient Perspectives Must Be Further Considered; Other Perspectives Should Also Be Added
ICER recently released guidelines on involving patients in the value assessment process, which is a promising development. At the same time, however, entities such as Avalere/Faster Cures and National Health Council have developed their own guidelines for assessing patient perspectives in value assessment frameworks.[20] ICER should further engage with patients, patient advocates, caregivers, and others to better understand and capture all potential impacts to patients and their networks, to include caregivers and families.

As we move into an era of adapting patient-centered value assessments[21] and establishing frameworks for patient-focused drug development and regulatory use of real-world evidence,[22] QALY should not be used as the sole outcome measure for assessing drug value. We believe the draft framework can and should be extended to capture patient, caregiver, provider, payer, and societal benefits and include how these metrics can improve quality measures such as hospital readmissions. Ultimately, value can be ascertained in the context of the "Triple Aim" for healthcare: (1) improving patient experience, (2) reducing healthcare expenditures, and (3) enhancing population health.[23]

ICER Framework Section #5.1: ICER will engage in a collaborative process to gather information with the intent of developing a template to provide information in its future reports on research, development and related costs related to new treatments for serious ultra-rare conditions.

Mallinckrodt Response:
Significant Concerns Exist with Attempting to Quantify Costs of Drug Development

[20] See e.g., http://avalere.com/expertise/life-sciences/insights/avalere-health-and-fastercures-release-version-1.0-of-the-patient-perspecti; and http://www.nationalhealthcouncil.org/patient-centered-value-model-rubric-released.
[21] NPC 2017: National Pharmaceutical Council http://www.npcnow.org/sites/default/files/npc-guiding-practices-for-patient-centered-value-assessment.pdf (accessed September 15, 2017).
[22] DCRI 2017: Duke Clinical Research Institute https://dcri.org/rwe-new-approach/ (accessed September 15, 2017).
[23] IHI 2017: http://www.ihi.org/Engage/Initiatives/TripleAim/Pages/default.aspx (accessed September 15, 2017).

Mallinckrodt has significant concerns regarding ICER's proposal to develop a template to collect information from manufacturers to provide information in its future reports on research, development and related costs related to new treatments for serious ultra-rare conditions.

First, such a template is unnecessary. For publicly traded companies, much of this information must be reported in the aggregate in disclosures to the Securities and Exchange Commission (SEC). Such redundancy would require a significant amount of resources, and as described more fully below, would be difficult to accurately capture and attribute to a particular drug. Moreover, publicly traded companies are subject to SEC rules relating to the release of information. Specifically, under Regulation FD, whenever a public company, or any person acting on its behalf, discloses material nonpublic information to certain enumerated persons, the company must disclose that information to the public.[24]

Second, significant practical challenges would make this information difficult, if not impossible, to capture. New drug development, particularly in early investigational stages, often occurs across a range of therapeutic areas, rather than on a single investigational compound. Thus, separating the research and development costs of any one product from the aggregated spending for all of a company's clinical development programs will be extremely complex, if not impossible. As an example, a company often researches multiple drug compounds in a therapeutic area (e.g., ALS) and multiple compounds for multiple disease states. Separating the research and development costs over multiple years of study further complicates the process. As well, pre-clinical phase investments are difficult to capture and assign to one particular product.

Moreover, the vast majority of compounds that enter clinical trials never become approved products. These development costs are absorbed by the entity or entities performing the trials and will not be captured, yet these are significant costs to the development of new drugs. In the precompetitive space, collaborative efforts exist in which companies share clinical trial information to speed drug discovery, which may reduce costs.[25] The ability to quantify those costs and allocate them to a single product or entity, however, will not be possible.

Investigational products often change ownership as a result of mergers, acquisitions, licensing, and joint development agreements that are common in the life sciences space, particularly for products to treat orphan diseases. This creates additional challenges to the development of a common "template," and limits the likelihood that the information ICER seeks can be captured, quantified, and translated into a value assessment framework for a single approved product.

As Scott Gottlieb, Commissioner of the FDA, recently acknowledged, drug development costs do not stop at launch, and in fact, continue to increase. In a recent speech he highlighted data from the Tufts Center for the Study of Drug Development, which found that between 2003 and 2013, the cost of developing a drug rose by 145 percent after correcting for inflation.[26]

Finally, much of the information sought is considered trade secret or confidential commercial or financial information that is expressly protected from public release under the Freedom of

[24] https://www.sec.gov/rules/final/33-7881.htm.
[25] http://www.transceleratebiopharmainc.com/about/.
[26] https://www.fda.gov/NewsEvents/Speeches/ucm575400.htm.

Information Act.[27] Companies may be very reluctant to share this highly sensitive information with ICER, particularly when ICER isn't prohibited from publicly disclosing this information. And, as noted above, SEC rules prohibit publicly traded companies from sharing nonpublic material information.

For all of the foregoing reasons, we do not support the collection of information related to research and development costs on the part of ICER, or the creation of a template to capture such data and information. We also believe it's highly likely that companies may be reluctant to share this information with ICER.

ICER Framework Section #6.1: During public meetings of ICER's appraisal committees, votes on "long term value for the money" of treatments for serious ultra-rare conditions will only be conducted if the base case estimate falls between $50,000 to $175,000. Treatments above $175,000 QALY would receive no value designation.

Mallinckrodt Response:
Mallinckrodt has significant concerns with the adoption of QALY, as described more fully above in our response to the proposed framework Sections 3.1-3.4.

* * *

Mallinckrodt appreciates the opportunity to comment on the Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions. We look forward to continuing to engage with ICER as it considers the public comments received on this proposed adaptation.

Sincerely,

Mark Tyndall
Vice President, Government Affairs, Policy & Advocacy
Mallinckrodt Pharmaceuticals

[27] 5 USC sec. 552(b)(4).

September 25, 2017

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

Re: Orphan Drug Assessment: Final Meeting Report and Proposed Framework Changes

Dear Dr. Pearson:

Merck & Co., Inc. appreciates the opportunity to provide comments to the proposed framework changes for orphan drug assessment. We share your interest in promoting health care systems in the United States that make the best use of available resources, informed by rigorous thinking and evidence, to care for all patients. We also embrace your willingness to solicit comments openly from stakeholders, and in the same spirit, we would like to offer our comments on the proposed framework. The comments below are organized by sections of your paper. We hope that this format makes our comments easy to incorporate.

1.1 ICER will consider using an adapted approach to value assessment for treatments that will be called a "potential major advance for a serious ultra-rare condition" if the three following criteria apply:

- **The treatment is envisaged for a patient population of fewer than 10,000 individuals**
- **There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals**
- **The treatment potentially offers a major gain in improved quality of life and/or length of life**

FDA defines rare diseases/disorders as those "that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug" (https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/ucm2005525.htm). ICER's definition of ultra-rare conditions appears to be reasonable in reference

to FDA's definition of rare diseases, although it is unclear how ICER will determine whether a treatment potentially offers a major gain in improved quality of life and/or length of life.

1.2 ICER will include in its initial draft scoping document a recommendation on whether a treatment meets the above criteria. Following formal public comment, ICER will make a final decision on whether the treatment meets these criteria and will therefore be appraised using an adapted approach.

The proposed adaptation sounds reasonable.

2.1 For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultra-rare conditions against historical controls will be highlighted.

We agree with ICER that scientific methodologies/standards for rating evidence should apply consistently across its reviews, whether a review is regarding an ultra-rare condition or not. Providing additional context and highlighting the challenges in generating evidence for treatments for ultra-rare conditions sounds to be a fair and appropriate action.

3.1 For assessment of cost-effectiveness of a potential major advance for a serious ultra-rare condition, ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.

The proposed adaptation is reasonable.

3.2 For these treatments ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from $50,000 per QALY to $500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.

Whether higher value should be applied to health gain obtained by people with ultra-rare conditions is in essence an ethical question more so than a scientific question. With the

proposed adaptation, ICER significantly expanded the WTP threshold range for treatments for ultra-rare conditions. There is no scientific criteria/method for judging whether the upper end of the range ($500,000 per QALY) is appropriate. The judgment is largely based on the stakeholder's interest or other strategic, political or socio-cultural considerations.

3.3 ICER will calculate a value-based price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

The proposed adaptation is reasonable. It is appropriate to use the same standard range to calculate price benchmark. Adding additional contextual language will help the broader audience understand the intricacy of value assessment.

3.4 When ICER 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. Instead, ICER will provide a crosswalk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found.

The proposed adaptation provides a practical approach to handling the situation where it is not feasible to translate measures of patient outcome into QALYs. However, in terms of the "crosswalk exercise", it is unclear how ICER will identify and select the "treatment and condition pair that is the closest clinical analogue." In addition, it is not clear how any contested points would be addressed by ICER in such cases.

4.1 For report sections on "other benefits and disadvantages" and "contextual considerations," ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

ICER's plan to enhance the sections on "contextual considerations" and "other benefits and disadvantages" is a positive move. However, this enhancement should not be restricted only to reports regarding ultra-rare conditions. We would recommend that ICER take the same action with its reports regarding other conditions.

5.1 ICER will conduct over the coming year a collaborative process through which it will seek to develop a template for providing information in its reports on the research,

development, and other relevant costs related to new treatments for serious ultra-rare conditions. Until this template is completed, ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.

Here ICER laid out a concrete plan for future improvement in cost data collection and manufacturers engagement. If executed as planned, these actions may enhance future value discussions thus make future ICER reports more solid. These actions should not be restricted only to reports regarding ultra-rare conditions. We recommend that ICER should take the same actions with its reports regarding other conditions.

6.1 During public meetings of ICER's independent appraisal committees, votes on the "long-term value for money" of treatments for serious ultra-rare conditions will be done according to the same procedures for other interventions, i.e. if the base case estimate falls between $50,000-$175,000 per QALY. However, for treatments of ultra-rare conditions, ICER will not assign any designation of value if the base case cost-effectiveness ratio is above $175,000 per QALY.

With the proposed adaptation for the situation where the base case estimate is above $175,000 per QALY, ICER implies that decision makers may make better value assessment by taking a broader consideration of other benefits, disadvantages, and contextual factors without an ICER-designated value rating. We agree with ICER on this point. In fact, the same logic also applies to the situation where the base case estimate falls between $50,000-$175,000 per QALY and even to ICER reviews on treatments for more common conditions. We recommend that ICER stop assigning QALY-dominated value ratings. Policy makers will be better served with information that captures a broader view of value and relevant contextual factors.

Once again, Merck appreciates the opportunity to provide feedback to ICER's Orphan Drug Assessment. We believe that these interactions are helpful to bring together multiple perspectives that will surely improve the articulation of value evidence in support of appropriate patient access to needed treatments.

Sincerely,

Elizabeth J. Cobbs, Ph.D.
Executive Director, CORE
Merck & Co., Inc.

Hemophilia Federation of America

National Hemophilia Foundation
for all bleeding disorders

September 25, 2017

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

Re: Proposed adaptation of the ICER value framework for the assessment of treatments with ultra-rare conditions

To Whom It May Concern:

The National Hemophilia Foundation (NHF) and the Hemophilia Federation of America (HFA) are national 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. Hemophilia A and B are rare, chronic bleeding disorders affecting approximately 20,000 individuals in the US. There are a number of even more rare factor deficiencies, such as factor I, II, V, VII, X, XI, XII and XIII deficiencies. We appreciate the opportunity to provide comment to the Institute for Clinical and Economic Review (ICER) on its proposed adaptation of the ICER value framework for the assessment of treatments with ultra-rare conditions. We believe this framework should be applied to treatments for all our small patient populations.

We are pleased to submit comments on a number of ICER's proposed adaptations in order as described in the framework:

1.1 – ICER will consider using the adapted value framework for ultra-rare conditions affecting fewer than 10,000 individuals; if indications are unlikely to expand beyond 20,000 individuals; and if the treatment potentially offers a major gain in improved quality of life and/or length of life

We are concerned that ICER is proposing to employ an arbitrary – and very low - number threshold rather than making an assessment as to the quality of the evidence for a particular condition before deciding whether the adapted framework is appropriate. We agree with those who argue that additional factors, such as severity and potential for a significant gain in quality or length of life, should be considered rather than just a number of patients. ICER has not sufficiently justified why the threshold is so low, nor why it would be implemented so strictly. We would ask that ICER allow for some flexibility in using the number threshold of 10,000 impacted individuals along with other factors in determining whether to use the adapted framework.

2.1 – ICER will use its regular approach to rating evidence but will provide "specific context" in its reviews of ultra-rare conditions.

We ask that ICER provide more detail about how the "specific context" information will be included in the review and how much weight that ICER will direct the independent reviewers to give this information as they vote on value at the public meeting. We appreciate that ICER will provide additional contextual information in its reviews of treatments for ultra-rare conditions but are concerned that it may be overlooked by payers or other stakeholders reading an ICER review.

4.1 – ICER will include a broader analysis regarding the effects of an ultra-rare treatment on the family, school and community.

We support that ICER will review a broader set of effects for ultra-rare treatments. Hemophilia and other bleeding disorders have significant effects not only on the affected person, but also his or her family, community, employer and the health care system. We encourage ICER to review the "infrastructure" of care not only for those conditions with no treatments, but all ultra-rare conditions. Finally, we ask that ICER provide more information about how it will incorporate this information in its reviews. It is unlikely that there will be high-quality evidence about the effects of a potential treatment on this broader group of outcomes, which are extremely important to patients and their families.

5.1 – ICER will develop a template to provide information regarding the costs a manufacturer incurred in developing the treatment.

We recognize that many stakeholders seek more information about the costs of research, development, marketing and profit involved in developing treatments, particularly for rare conditions. However, we are concerned about ICER incorporating this information in its reviews since it will be difficult to gather and as ICER notes, "there is a significant risk of false assumptions and unintended consequences." Moreover, it is not clear that a manufacturer's profit should affect the value of a given treatment for a patient, family, or even a health system. We encourage ICER to include all stakeholders, including patients, manufacturers, and payers, if it moves forward with developing this template.

We appreciate the opportunity to provide feedback on ICER's framework for ultra-rare conditions. Please contact Michelle Rice, NHF's Senior Vice President for External Affairs and Katie Verb, HFA's Director of Policy & Government Relations with any questions.

Sincerely,

Val Bias
Chief Executive Officer
National Hemophilia Foundation

Kimberly Haugstad
President & CEO
Hemophilia Federation of America

September 25, 2017

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

Re: ICER Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions

Dear Dr. Pearson:

On behalf of the 30 million Americans with one of the nearly 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Institute for Clinical and Economic Review (ICER) for the opportunity to provide comments on the Institute's "Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions."

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

We are committed to fostering an ecosystem that encourages the development and accessibility of safe and effective therapies for rare disease patients. We are excited by the advent of value frameworks, and believe that value frameworks, if developed collaboratively and used responsibly, can provide objective analysis for assessing the value of therapeutic interventions.

Rare diseases are largely understudied, misunderstood, and ignored due to the inherently small patient populations of each rare disease. It is for these reasons that Congress, state legislatures, and Federal and state regulatory bodies have recognized that rare diseases require a specialized, unique approach. Congress passed the Orphan Drug Act of 1983 and the Rare Diseases Act of 2002. Further, state legislatures across the country are creating Rare Disease Advisory Councils to advise state governmental bodies on the unique needs of the rare disease patient community. Finally, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) have created offices dedicated to rare disease research and drug development.

We applaud ICER for continuing this institutional recognition and adaptation by putting forward an amended value assessment framework for rare disease healthcare interventions. However, while we support several of the proposed changes ICER outlines within its adapted framework, we are very concerned with other approaches ICER has decided to pursue.

The following comments are structured using the outline of ICER's proposed adapted framework.

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1.1. ICER will consider using an adapted approach to value assessment for treatments that will be called a "potential major advance for a serious ultra-rare condition" if the three following criteria apply:

- **The treatment is envisaged for a patient population of fewer than 10,000 individuals**
- **There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals**
- **The treatment potentially offers a major gain in improved quality of life and/or length of life**

NORD is very concerned with ICER's proposed division of rare diseases into ultra-rare and non-ultra-rare conditions, and opposes this proposal. For decades, NORD has opposed efforts to create an ultra-rare category in various settings. For example, NORD has opposed creating an ultra-orphan category within FDA regulatory review of orphan therapies, public and private reimbursement policy for orphan therapies, and incentives for orphan drug development. Invariably we have asserted that creating an ultra-orphan subcategory will do more harm to the rare diseases that do not fall within that category than good for the rare diseases that do.

In addition, we are not convinced by ICER's rationale that,

> "only when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation".

We find this claim baseless and unfounded, and the lack of any citation or outside justification only furthers our conviction. There are many factors that contribute to the difficulty in evidence generation for orphan therapies, and we are confident they do not start and stop at the 10,000 prevalence number. For example, many diseases with prevalences above 10,000 are even more difficult to develop therapies for due to the heterogeneity of the manifestation, progression, and severity of the diseases, as well as the variability of treatment effects.

We also strongly disagree with ICER's assertion that "application of adapted methods of value assessment are not needed for the majority of 'orphan' drugs as defined by the Orphan Drug Act, as sufficient patient numbers are usually available for 'routine' clinical trials, and outcome measures are likely to be relatively standardized and well-documented." Again, we disagree with this unsubstantiated claim. Congress and FDA have long recognized the unique challenges of developing orphan therapies above population sizes of 10,000 individuals by enacting and implementing various incentives and regulatory practices that do not disqualify diseases with over 10,000 individuals. For ICER to make this claim, it is directly in contrast with every other institution in the United States that sets policy for the rare disease community.

It also makes little sense to us to require the unlikelihood of future expansion of indications in order to qualify for the adapted framework. The future prospects of a therapy's use have nothing to do with the current evidence that FDA or ICER have to consider. If a therapy is approved for a very small patient population, it is accompanied with all of the characteristics that ICER itself identifies as requiring an

adapted approach regardless of future expansion of indications. To apply this arbitrary requirement goes against ICER's very own logic and reasoning.

We strongly urge ICER to reconsider this approach outlined within this section. We encourage ICER to abandon use of an arbitrarily created subdivision of the rare disease patient community, and instead use the well-recognized and established definition for a rare disease already in existence: 200,000 or fewer individuals with the disease in the U.S.

2.1 For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultrarare conditions against historical controls will be highlighted.

We again are concerned with the approach enumerated within this section. We appreciate ICER's recognition of the "potential challenges of generating evidence for [ultra-orphan] treatments." But we are concerned that ICER is relegating these unique circumstances to merely "context" within their reports, without any integration into the methodology of the value assessment framework, will demote these critical considerations to a lower standard of evidence, and result in coverage decision makers ignoring them altogether.

After attending the Orphan Drug Assessment and Pricing Summit on May 31, 2017, it became clear to us that many of the stakeholders representing the insurance industry simply wanted a final number to base their coverage decisions on. By not including these crucial considerations into the methodology, ICER is allowing insurers to ignore these considerations by providing them with an assessment that does not include them.

Providing context within the final report is insufficient. Instead, ICER should integrate these considerations into the quantitative methodology of the comparative clinical effectiveness assessment.

3.2 For [serious ultra-orphan] treatments ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from $50,000 per QALY to $500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.

We support ICER's decision to expand its willingness-to-pay threshold from $50,000 per QALY to $500,000 per QALY. This is a valid method to incorporate the well-established higher societal valuation of therapies for rare diseases. However, we again request that this adjustment is made for all orphan therapies, not just a small ultra-orphan subset.

3.3 ICER will calculate a value-based price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special

weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

We are disappointed that ICER has chosen against amending its standard value-based price benchmark for orphan therapies. Again, ICER elects to use "language in all report formats" to inform decision makers rather than incorporating these critical considerations into the quantitative methodology.

Once again, we are concerned with ICER relegating the special circumstances in which orphan drugs are developed to easily-ignored qualitative report language. We again urge ICER to incorporate these considerations into the methodology itself. It was the insurance industry's input during the Orphan Summit that, "suggested that it would be preferable to remain consistent in the use of $100,000 to $150,000 per QALY." This preference did not originate from the patient or provider community.

ICER's preference for simplicity and consistency over accuracy and inclusion of nuance is concerning. Even though amending the value-based price benchmark to consider the unique circumstances of orphan drug development and reimbursement is difficult, we urge ICER to pursue this nonetheless.

3.4 When ICER 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. Instead, ICER will provide a crosswalk to a cost consequence price for a treatment and condition pair that is the closest clinical analogue that can be found.

We hope that ICER can provide additional information on when and how this determination would be made, and how exactly it plans to "provide a crosswalk to a cost consequence price for a treatment and condition pair that is the closest clinical analogue that can be found." At this time, we do not feel that we have enough information on this method to adequately comment.

4.1 For report sections on "other benefits and disadvantages" and "contextual considerations," ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

We commend ICER for its plan to "include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. NORD has long held that the societal benefits of an orphan therapy should be included within any assessment of its value. While we prefer these values to be included quantitatively within the assessment of the therapy, we are encouraged that ICER is broadening its focus to include as many of the therapy's positive impacts as possible.

We are particularly pleased that,

> "ICER reports will seek input from patients and clinical experts on the potential impact of a new treatment on the entire "infrastructure" of care, including effects on screening for affected

patients, on the sensitization of clinicians, and on the dissemination of understanding about the condition that may revolutionize how patients are cared for in many ways that extend beyond the treatment itself."

We thank ICER for this important step forward. However, we ask that ICER reexamine their patient participation guide and amend it appropriately to ensure this information can be adequately collected. As it currently stands, ICER's process for including the patient community is far too expedited for many patients and patient organizations to participate. Three-week comment periods for dense and esoteric ICER documents is far too short a time for a small rare disease patient organization to contribute. If ICER intends on making a concerted effort to include as many "other benefits and disadvantages" as possible, it must account for the limitations of the small communities that can offer such data and expertise.

5.1 ICER will conduct over the coming year a collaborative process through which it will seek to develop a template for providing information in its reports on the research, development, and other relevant costs related to new treatments for serious ultra-rare conditions. Until this template is completed, ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.

While we are not opposed to this effort moving forward, we are concerned with how it may impact the valuation of orphan therapies. More specifically, we believe a "fair price" and a "price that reflects the value of the treatment" are two different concepts. Assessing a therapy's value should rest solely on the benefits it brings to the individual, the healthcare system, and society as a whole with the consideration of the unique nature of rare diseases and orphan drugs integrated within. We are unsure how the financial investment a company makes into developing the therapy impacts the value it then offers to society.

We encourage ICER not to conflate the two topics, and to focus on the valuation of therapies rather than expand its scope into issues of fairness.

6.1 During public meetings of ICER's independent appraisal committees, votes on the "long-term value for money" of treatments for serious ultra-rare conditions will be done according to the same procedures for other interventions, i.e. if the base case estimate falls between $50,000-$175,000 per QALY. However, for treatments of ultra-rare conditions, ICER will not assign any designation of value if the base case cost-effectiveness ratio is above $175,000 per QALY.

While we are appreciative of ICER's proposal to "not assign any value rating to ultra-rare treatments if the base-case cost-effectiveness ratio exceeds $175,000 per QALY," we are concerned that ICER will be using the same cost-effectiveness range as they do with all other therapies. This is another circumstance where we request ICER to consider changing its quantitative methodology for determining value rather than depending on qualitative conjecture.

We thank ICER for the opportunity to comment, and we look forward to working with ICER to accurately and collaboratively assess the values of orphan therapies. For questions regarding

NORD or the above comments, please contact me [contact information redacted for posting. Thank you in advance for your consideration.

Sincerely,

Paul Melmeyer
Director of Federal Policy

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

September 25, 2017

Steven D. Pearson, MD, MSc
President
Institute for Clinical and Economic Review
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Submitted via email: publiccomments@icer-review.org

RE: Comments on the "Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions"

Dear Dr. Pearson,

On behalf of Pfizer Inc, I am pleased to submit this letter in response to the call for comments issued by the Institute for Clinical and Economic Review (ICER) regarding proposed adaptations to ICER's value framework for the assessment of treatments for ultra-rare conditions.[1] We appreciate your willingness to solicit feedback from all relevant stakeholders with respect to this important topic.

As a leading biopharmaceutical company, Pfizer is dedicated to the discovery and delivery of high value therapies across a variety of disease areas. Our scientists have and continue to make significant contributions to medical research, and we strive to set the highest standard for quality, safety, and value in the discovery, development, and manufacturing of health care products.

Pfizer has a strong interest in the ongoing policy deliberations regarding the measurement of value in health care. We have sought productive and consistent engagement with ICER and other stakeholders about how to appropriately measure value across the spectrum of healthcare products and services. We have a particular interest in helping to further conversations around the most appropriate and accurate measures of value for rare, ultra-rare, or orphan diseases (hereafter simply referred to as "rare disease"), as we believe there are significant challenges in reconciling existing population-level value assessment methodologies with the

[1] Institute for Clinical and Economic Review. Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions. Available at: https://icer-review.org/material/odaps-proposed-changes. Accessed August 29, 2017.

varied healthcare contexts and highly individualized patient-level treatment decisions faced by rare disease patients, their families, and their clinicians.

The concept of "patient centricity" has taken on growing importance in ongoing conversations about value in healthcare. We believe that applying a patient-centric lens in the assessment of value of treatment for rare disease is especially important, because (a) the health consequences of rare diseases are often debilitating or deadly, (b) the manifestation of the burden for a given disease is often unique to individual patients and their caregivers, and (c) the healthcare needs of patients with rare diseases are underrepresented in healthcare policy discussions, which are typically focused on broader population needs.

Thus, the use of a population-based approach (such as the cost per quality-adjusted life year, or QALY) to assess the value of treatment for rare disease is fundamentally flawed, because the assessment principles of such approaches inherently under-value the unique considerations appropriate for rare disease patients. By their nature, population-based approaches will always bias against the value of innovation in rare disease – even if a treatment offers significant clinical value – given the small patient populations treated and the relatively minimal impact to average direct health care costs. New and innovative approaches to assessment of value of rare disease treatment that are based on their value to the individual patients, their caregivers and society are critically needed.

While we appreciate ICER's efforts to adjust its current population-focused value assessment framework for ultra-rare diseases, the current proposal offers minimal adaptations and ultimately does not recognize the fundamental challenges associated with rare disease evidence development and evaluation. In fact, much of the proposed adaptation document reads as a justification to use key elements of ICER's standard approach to value assessment in rare diseases.

Therefore, we ask that ICER reconsider its approach and broaden its perspective on assessing treatment value in rare diseases, as other organizations (e.g., EURORDIS) have done. It is important to more comprehensively address not only the crucial patient-centric view of value, but also the inherent evidence constraints and methodologic challenges that make value assessment in rare disease distinct from conventional and broader population health approaches. Otherwise, ICER's rare disease reports are likely preordained to underappreciate the importance and value of potentially transformative treatments.

In our comments that follow, we have highlighted a number of key recommendations that we ask ICER to consider, as it seeks to reframe its approach to the evaluation of value of treatments for rare disease conditions.

<u>Recommendation</u>:
ICER should develop and present for public comment additional details regarding the "other benefits and disadvantages" and "contextual considerations" that it will highlight in its value assessments.

A critical component of ICER's proposal relates to the "other benefits and disadvantages" and "contextual considerations" sections of its value assessment report. These sections are critical to ensure that the unique needs of patients with rare disease are appropriately represented. Further, these two sections have the potential to provide readers of ICER reports with information that can help frame value assessment in an appropriately patient-centric manner.

We are concerned that in its current proposal, ICER does not offer specifics on what elements / variables might be included in these two sections. Given the relative importance of these two sections in the context of rare diseases, we ask that ICER convene a discussion with stakeholders to develop a rubric around what elements should be considered in them. We also ask that ICER offer all stakeholders an opportunity to provide separate public comment on this new rubric. Once these two steps have been completed, we ask that ICER consistently apply this rubric, allowing for sufficient flexibility to account for differences across conditions.

<u>Recommendation</u>:
ICER should reevaluate which conditions may be considered under an alternative value framework, with a greater focus on availability of evidence as opposed to population size.

ICER suggests that use of an adapted approach to value assessment could be limited to conditions that meet three criteria related to population size and potential gains in patient quality or length of life. Although ICER reviews various definitions of rare disease in its document, it does not offer a clear, scientifically-backed rationale for its population-based cutoffs. The document simply states that "[o]nly when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation".[1] No explanation or other substantiation for this conclusion is offered. ICER also does not articulate what might constitute "major" or "substantial" gains in patient quality or length of life..

The primary challenge with developing a value assessment for rare disease relates to the availability of high quality evidence at the time of registration and market authorization. Because of the small population sizes, study design constraints and long-term outcome uncertainties, it is not realistic to use population size alone as hard and fast criteria for when an alternative approach to value assessment may be appropriate.

We recommend that ICER fundamentally reconsider its population size approach to determining when an alternative framework should be used in value assessment.

We instead urge ICER to develop a set of criteria that recognize the evidence availability constraints in rare disease at the time of registration and market authorization. These criteria should include elements such as sample size, design and analytic characteristics of the clinical trials, and could also take into account the validity and reliability of the study endpoints, the availability and value of other sources of evidence, unmet needs, and the overall quality of the regulatory and reimbursement submission dossiers (including plans for ongoing evidence development to address key clinical uncertainties and value evidence elements post-approval). We would be pleased to work with ICER and other stakeholders (such as methodology experts and patient advocates) to develop this set of criteria based on consensus discussions and to test its applicability and use.

Recommendation:
ICER should reconsider its approach to evidence rating for rare disease.

ICER utilizes its Evidence Rating Matrix[2] to assess the rigor of the scientific studies used in its value assessment reports. In the current proposal, ICER indicates that it does not believe that changing the approach to evidence rating is necessary and instead suggests that the provision of "specific context regarding the acknowledged challenges that often arise in evidence generation" will sufficiently allow decision-makers to understand the value of the studies reviewed.

We disagree with ICER's rationale for utilizing the existing Evidence Rating Matrix in rare disease reports because it does not address the critical differences in the types and volume of data that are available in rare disease. Some of the key development challenges in rare disease include:

- Patient recruitment: The limited number of patients and their geographic dispersion especially for very rare diseases can lead to challenges with trial management and recruitment. This can result in long patient recruitment phases and less stringent inclusion/exclusion criteria. Additionally, it can be difficult to adequately power studies to evaluate treatment efficacy.

- Patient heterogeneity: Many rare diseases have significant levels of patient heterogeneity. This is especially true of conditions where there is a wide degree of variability in genetic mutations linked to the disease. The variation in expressed phenotypes for many rare diseases, combined with the small research base, often makes it difficult to classify and diagnose patients. This can also lead to substantial variability in the baseline characteristics and response to therapy within a clinical trial, which can undermine trial results.

- Selection of trial endpoints: Many rare diseases are not well characterized; the general lack of available natural history data makes the design of trial

[2] Ollendorf D and Pearson S. ICER Evidence Rating Matrix: A User's Guide. Available at: http://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf. Accessed September 7, 2017.

endpoints challenging. It is not uncommon for pivotal trials to rely on disease response scales that are not used in regular practice and have not been thoroughly validated. In addition, comparative historical data is often lacking. This raises challenges for extrapolating trial endpoint data into estimates of the impact on disease progression.

- Uncertain population prevalence: Given the limited research in the area of rare diseases as a whole, there is high uncertainty associated with prevalence estimates for rare diseases. This is especially problematic when a disease has a broad spectrum of severity and the drug is indicated for the most severe patients only. In these cases the data to determine the prevalence of the most severe patients can be especially difficult to obtain.

- Trial duration: Given the challenges with patient recruitment and the unmet needs in the patient population, rare disease medicines are often approved with Phase II data and the associated endpoints. In such cases, longer term data on safety and efficacy are collected as post approval, and in EU, post reimbursement commitments.

ICER's Evidence Rating Matrix takes a traditional approach to assessing the rigor of studies and relies on two variables: comparative net health benefit and level of certainty in the evidence. In the case of rare diseases, both variables would likely be very difficult to measure given the development challenges highlighted above. Given the relative lack of data for rare diseases, the confidence intervals around net benefit estimates are likely to be large, making it difficult to detect statistical differences in benefit across treatments. Similarly, a dearth of data would make it challenging to make claims about certainty in level of evidence. As such, utilizing the existing Evidence Matrix approach will simply result in many (if not all) reviews concluding that there is insufficient evidence – offering no solution for understanding value to patients and other stakeholders.

It is important to note that regulators and value assessment bodies worldwide have recognized the inherent challenges of evidence development in rare disease, and have, in many cases, made adaptions for the appraisal of uncertainty and value for these conditions. For example, in France, early access programs for rare disease medicines are available prior to marketing authorization, with the opportunity to engage in early dialogue over the structure and type of the evidence to be generated.[3] We suggest that ICER undertake a review of such tactics, and consider reframing its approach to address the practicalities of evidence generation and evaluation by adopting some of the best practices. Pfizer colleagues have developed a deep understanding of these alternative approaches, and we would welcome an opportunity to share our thoughts and learnings with ICER.

[3] Balasubramanian G, Morampudi S, Chhabra P et al. An overview of Compassionate Use Programs in the European Union member states. Intractable Rare Dis Res. 2016; 5(4): 244–254.

<u>Recommendation</u>:
ICER should replace its current QALY-based evaluation and utilize a broader multi-criteria stakeholder approach to value assessment.

The current ICER value framework calculates incremental cost effectiveness using the QALY measure. The significant methodological shortcomings of the QALYhave been well documented, both by researchers[4] and ICER itself[5]. Yet ICER continues to utilize the QALY in its framework, arguing that that there is "no superior overall measure of comparative net health benefit".[5] We maintain that the absence of a better measure is not a valid rationale for use of a clearly flawed one.

Our concerns about the use of the QALY are even more significant in the area of rare diseases. Specifically we note that:

- Relatively small sample sizes, a preponderance of single-arm trials and the inherent uncertainties in rare diseases make it impossible to meaningfully aggregate health-related quality of life data, which is the basis of the QALY calculation.

- QALYs fail to account for non-health benefits. Non-health benefits and in particular, societal benefits, such as a faster return to work, improved ability to act as caregiver or better school performance are not factored into QALY calculations despite being of potentially considerable importance, especially in rare diseases.

- The QALY is not sensitive enough to measure small but clinically meaningful changes in health status or utility. Such changes are particularly applicable and central in rare disease.

- QALY utility scores fail to account for a variety of additional factors such as severity of the initial health state and disease prevalence. These elements are especially important in rare diseases.

- A QALY-based economic assessment is inherently biased against rare disease therapies that may involve higher upfront costs, but offer great potential for long term health benefits across many patient-centric value domains.

- Approaches that adopt a QALY threshold to determine value are binary and not patient centric, because they fail to recognize that there may be wide differences in what patient populations may deem to be acceptable cost-effectiveness thresholds.

[4] Pettitt DA, Raza S, Naughton B, et al. The Limitations of QALY: A Literature Review. J Stem Cell Res Ther. 2016; 6(4) 1-7.
[5] Pearson S. A framework to guide payer assessment of value of medical treatments. Available at: http://icer-review.org/wp-content/uploads/2014/01/Value-Assessment-Framework-DRAFT-6-13-14.pdf. Accessed August 30, 2016.

Given the acknowledged limitations of the QALY, we urge ICER to move away from a threshold-based approach to its cost-effectiveness analysis. ICER's current proposal to increase its threshold limits to $500K/QALY will not address the fundamental limitations of the QALY as a measure.

We ask that ICER use this opportunity to consider alternative approaches to value assessment that are more suitable for rare diseases. In particular, we ask that ICER consider how proposals related to multi-criteria value assessment could better represent and account for the complexity of stakeholder value perspectives and societal issues associated with rare diseases. Our experts have developed a strong understanding of such alternatives, and we would welcome an opportunity to discuss how these approaches might be adopted by ICER.

Recommendation:
ICER should reconsider its use of a "value-based price" benchmark given the limitations of the QALY measure.

ICER's calculation of a "value-based price benchmark" relies on QALY-based cost-effectiveness thresholds to derive a pricing estimate that fits within the confines of these thresholds. In its reports, ICER presents the value based price benchmark as a reliable measure of what a treatment should cost, given its inherent value to stakeholders. As we have noted previously, ICER does not explicitly acknowledge the myriad set of assumptions that were built into this estimate, nor does ICER acknowledge that sensitivity analysis for any one of the variables underlying the estimate could lead to dramatic shifts in what might be a "value-based price" for a given product.

We strongly recommend that ICER discontinue its calculation of this "value-based price benchmark" for rare disease treatments, as it is essentially a theoretical construct that is not relevant to the broader debate around patient value. ICER itself has recognized that estimating a price benchmark for rare diseases may be especially challenging, and in the proposed adaptation, has offered to "…provide a crosswalk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found" for situations in which a QALY-based approach cannot be used. Rather than make these types of exceptions for situations that are common for rare diseases, we recommend that ICER focus more deliberately on understanding the relevant elements of value and preferences that matter most to patients.

Recommendation:
ICER should clarify the rationale behind its planned request for research and development costs associated with rare disease treatments.

ICER states that it intends to "…develop a template for providing information in its reports on the research, development, and other relevant costs related to new treatments for serious ultra-rare conditions". ICER's rationale for collecting this data

relates to pricing of innovative treatments, but it is not clear if and how ICER plans to use these data in its value assessments.

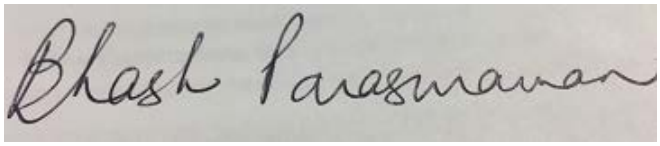
It seems that ICER may seek to correlate the cost of drug development for rare disease to price for rare disease therapies. This suggests a fundamental misunderstanding of both the research and development process and the value-related factors that are considered in determining a price for an innovative rare disease treatment. We recommend that ICER clarify how and why it believes these data may be relevant to a discussion of clinical and patient value.

Summary

Pfizer is pleased to have the opportunity to submit comments in consideration for the proposed adaptation of ICER's value framework for rare disease. As noted at the beginning of this letter, Pfizer continues to have a strong interest in engaging all relevant stakeholders on the most appropriate ways to define and demonstrate the value of healthcare interventions within the unique area of rare diseases.

We remain very interested in ICER's approach to value assessment for rare disease treatments and hope that our comments are useful as the organization seeks to revise its proposal. We would welcome an opportunity to discuss our comments with you in additional detail.

Kind regards,



Bhash Parasuraman
Vice President, Rare Disease, Patient and Health Impact
Pfizer Inc.

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

Institute for Clinical and Economic Review
Steven D. Pearson, MD, MSc, FRCP
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Re: Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions

September 25, 2017

Dear Dr. Pearson,

On behalf of Parent Project Muscular Dystrophy (PPMD), we are pleased to submit the following comments on the Proposed Adaptation of the ICER Value Framework for the Assessment of the Treatment for Ultra-Rare Conditions.

Introduction to PPMD

PPMD is the world's largest organization focused on ending Duchenne muscular dystrophy. Duchenne muscular dystrophy is the most common fatal genetic disorder diagnosed in childhood, affecting approximately 1 in every 4000 live male births (about 20,000 new cases each year worldwide). Because the Duchenne gene is found on the X-chromosome, it primarily affects boys; however, it occurs across all races and cultures. Duchenne is a progressive disease diagnosed in early childhood that affects skeletal muscle and the cardiac and pulmonary systems. Children diagnosed with Duchenne typically live only into their 20s. In short, Duchenne is 100% fatal. PPMD is the leading voice for the Duchenne Muscular Dystrophy community and, as such, is actively engaged in all stages of advancing medical innovation for our families. Our PPMD community is comprised of clinical and scientific experts and an engaged and diverse network of patient families.

PPMD has long been committed to ensure that patient experiences are incorporated into the drug development infrastructure and access ecosystem in a meaningful way. The advent of the Patient Focused Drug Development (PFDD) provisions within the 2012 Prescription Drug User Fee Agreement (PDUFA V) and corresponding FDA Safety & Innovation Act (FDASIA) aligned perfectly with the dawning of a new day for our Duchenne community – one in which basic laboratory breakthroughs had evolved into clinical trials, enabling the Duchenne pipeline of experimental therapies to become more robust than ever. PPMD immediately embraced the opportunities presented to us

through PDUFA V and have worked over the past few years to evolve the science of patient input and advance the field of Patient-Focused Drug Development.

Since that time, we conducted the first-ever scientifically rigorous survey of parents of Duchenne patients to obtain quantitative evidence as to their views on benefit-risk and are now conducting subsequent expansions of our patient-preferences studies into a broader caregiver demographic and young people living with Duchenne. We have published a series of white papers analyzing PDUFA through the lens of the Duchenne community including *PPMD's Putting Patient's First* and *PPMD's Benefit-Risk Assessments in Rare Disorders* publications. We also have led a comprehensive and multi-stakeholder effort to prepare draft guidance to industry developing Duchenne therapies. This PPMD-led guidance, *"Guidance for Industry Duchenne Muscular Dystrophy Developing Drugs for Treatment over the Spectrum of Disease"* was submitted to FDA in June 2014 and – along with a Duchenne Community Policy Forum convened by PPMD in December of 2013 - was the foundation used by the agency to develop its own draft guidance on the same topic issued in June of 2015 entitled, *"Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment."*

In addition, we have been one of the first patient communities to use scientifically validated preference methods to measure patient and caregiver preferences. By partnering with social scientists and health economists from Johns Hopkins University, we have completed two patient preference studies involving subsets of the Duchenne community and are in the midst of conducting two additional studies. In 2016, to further advance the field of PFDD and to ensure that the lessons that have been learned to date are shared broadly -- the Biotechnology Industry Organization (BIO) and PPMD convened the world's leading experts in the science of patient preferences to develop and publish *Key Considerations for Developing and Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study.*

PPMD and Value Frameworks

In November of 2015, ICER conducted routine forecasting and announced that three (3) Duchenne therapeutic products would be reviewed in the coming months. At that time, PPMD became familiar with the ICER value framework and reached out to ICER to understand how we could be of assistance during the review process and report. We also wanted to understand whether PFDD data and rare disease considerations would factor into the reviews. While the regulatory proceedings around those products altered the review timelines, PPMD's engagement with ICER around the unique challenges and opportunities within the rare disease community continued.

Parent Project Muscular Dystrophy JOIN THE FIGHT. END DUCHENNE.

Ultimately, the engagement with ICER evolved into our participation in the Working Group which helped to inform the *ICER Orphan Drug Assessment & Pricing Summit* (May 2017). Based on this cumulative experience and advice from our community experts, the following is PPMD's commentary on the "Proposed adaptation of the ICER framework for the assessment of treatments for ultra-rare conditions."

Commentary on Proposed Adaptation of the ICER Framework for the Assessment of Treatments for Ultra-Rare Conditions

1.1 With respect to ICER's proposed adapted approach and criteria for treatments that will be considered a "potential major advance for serious ultra-rare conditions":

Overall comment:

ICER language:
…drugs as defined by the Orphan Drug Act, as sufficient patient numbers are usually available for "routine" clinical trials, and outcome measures are likely to be relatively standardized and well-documented (page 3)

PPMD comment:
Endpoints are not standardized nor are they well documented in rare disease patient populations. This is why sponsors conduct observational studies and sometimes try to repurpose outcome measures used in other settings in rare disease populations despite not knowing how they will perform (i.e., 6MWT in Duchenne is a measure previously validated in respiratory trials by the ATS). An excerpt from FDA's Guidance for Industry related to Duchenne addresses this issue:

"There is no defined set of required or recommended clinical outcome measures for studies in dystrophinopathies. Although existing outcome measures that have been developed for clinical trials and/or clinical care in dystrophinopathies or related conditions may be appropriate, FDA will also consider proposals for the use of new outcome measures that are capable of measuring clinically meaningful effects in patients. Sponsors are encouraged to propose, and, if necessary, develop, endpoints that can be used to validly and reliably assess patients with a wide spectrum of symptoms and disease stages. FDA should be engaged by a sponsor early during the selection and/or development of efficacy endpoints. Assessment of multiple efficacy endpoints should be included when feasible, to characterize the breadth of effects on dystrophin-related pathologies, including skeletal, respiratory, and cardiac muscle function, even if

the study primary endpoint is only one of these measures."
(Efficacy Endpoints, lines 217-227, *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry*, FDA, CDER, June 2015)

This poses a challenge even for patient populations >10,000 and adds to the cost of development, especially when evidence from small studies is inconclusive.

1.1 ICER will consider using an adapted approach to value assessment for treatments that will be called a "potential major advance for a serious ultra-rare condition" if the three following criteria apply:

- **The treatment is envisaged for a patient population of fewer than 10,000 individuals**
- PPMD does not support the divergence from the definitions imbedded within the Orphan Drug Act and sub-categorization of rare disease communities into rare and ultra-rare communities based on the prevalence of >10,000. The Orphan Drug Act defines a rare disease as one the affects less than 200,000 Americans. PPMD recommends that ICER adopt a standard consistent with the law.

- **There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals**
- Even in the instance of 2 individual rare diseases that might benefit from the same therapy, each would require their own individual development pathway on the part of the sponsor which would include costly and extensive safety and efficacy studies.

- **The treatment potentially offers a major gain in improved quality of life and/or length of life**
- In the instance of approvals derived through the accelerated approval, this third item, as currently defined, becomes subjective and underscores the importance of the issue of the timing of when valuations are conducted. In the accelerated approval pathway, approval is based on the achievement of a surrogate endpoint in which clinical benefit is reasonably likely. In our experience, modest effects among therapies designed to address unmet medical need in rare conditions is not unusual and represents an important stepping stone for future development. In this criteria, how is "potentially" or "major gain" defined – and by whom?

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2.1 **For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultra- rare conditions against historical controls will be highlighted.**

PPMD comment
Regarding "arguments to justify high price" (page 4)

- We believe the ICER Framework should consider the cost of required commitments and follow up measures that may be required when development programs are accelerated. These are key regulatory commitments that must be met and their execution may be no less challenging and critical post approval.

ICER language

"Following stakeholder input, ICER believes that decision-makers will be better served by retaining consistency in the application of ICER's EBM matrix and its approach to judgments on the magnitude of health benefit and level of certainty. Establishing artificial criteria for number or type of studies, or trying to specify a different threshold of uncertainty for treatments of ultra-rare conditions would be more likely to obscure important distinctions related to these treatments than to aid in consistency and transparency of decision-making.

However, informed by input from stakeholders, ICER will consider in its own judgments, and will highlight in the report, specific context regarding the acknowledged challenges that often arise in evidence generation for these treatments. Decision-makers should be given context to allow them to understand what might be viewed as feasibility constraints on manufacturers in generating robust evidence packages, and should know the historical context of the evidence produced for regulators and payers for similar treatments in the past. "

PPMD comment

Our concerns with retaining one matrix for all products include:

- The use of surrogate endpoints in the case of accelerated approval yielding little

clinical evidence at the time of approval impacting the conceptual confidence interval;
- The timing of the valuation; and
- The lack of specificity around the "stakeholders" who will inform ICER's judgments.

Moreover, by positioning the consideration of factors impacting ultra-rare, or in our recommended approach, rare conditions, after the matrix is completed, we believe there will be little to any recognition of the payer community to these crucial considerations. Any appropriate adjustments for rare disease therapies should be incorporated into the matrix itself.

In summary

PPMD is grateful to ICER for its continued commitment to improvement and engagement of the patient community in the value assessment framework process. We understand that valuation of emerging products is a complex science and that, in the context of rare, progressive diseases with few treatment options, the complexity increases.

What we ask ICER to allow for within your framework is an algorithm that is inclusive of the expertise, experience and evidence around patient-preference – and the trade-offs and considerations patients make when seeking treating options. We hope that we have provided some meaningful input for you to consider both through our engagement leading up to and throughout the Summit and within our comment here. We stand ready to continue to collaborate with you. For more information about any of the resources referenced within this comment or Duchenne community engagement, please feel free to contact Annie Kennedy PPMD's Senior Vice President Legislation & Public Policy [contact information redacted for posting].

Sincerely,

President & CEO
Parent Project Muscular Dystrophy

Plasma Protein Therapeutics Association

25 September 2017 **BY E-MAIL**

Plasma Protein Therapeutics Association Response to the public consultation of the Institute for Clinical and Economic Review on the "Proposed adaptation of the ICER value framework for the assessments of treatments for ultra-rare conditions"

Challenges of the Plasma Protein Therapeutics sector with regard to traditional methods for the value assessments of medicines

The Plasma Protein Therapeutics Association (PPTA) represents the private sector manufacturers of plasma-derived and recombinant analogue therapies, collectively known as plasma protein therapies and the collectors of source plasma used for fractionation. These therapies are used by small patient populations worldwide to treat a variety of (ultra-)rare diseases and serious medical conditions, such as haemophilia, primary immunodeficiency, alpha-1 antitrypsin deficiency, chronic inflammatory demyelinating polyneuropathy etc. In some indications, they have no treatment alternatives.

PPTA fully supports the vision that orphan disease treatments require a separate approach to evidence generation and assessment of their clinical and cost-effectiveness and therefore welcomes establishing of an alternative framework in consultation with stakeholders. There are several major obstacles to the application of traditional assessment frameworks to orphan medicines:

- Small patient populations imply that adequate enrolment numbers are often unfeasible.
- Inadequate understanding of the pathogenesis of a disease and/ or of the mechanism of action of a drug cause difficulty in clinical trial design, i.e. definition of relevant endpoints, treatment pathways and appropriate trial duration.
- Frequently severe, disabling or life-threatening conditions exclude the chance of comparison of the treatment effect to the effect of no-treatment.
- Insufficient statistical power to detect clinically meaningful outcomes from often small-scale trials.
- Evidentiary uncertainty introduces challenges to the prospective modeling of the trial results in the future and a robust cost-effectiveness analysis.
- The necessity to earn back the high R&D investments in medicines used by a limited group of patients causes high price and incremental cost-effectiveness ratios which sometimes lie high above the willingness-to-pay thresholds.

The challenges to the industry are even bigger when it concerns orphan biologics, especially those produced from human blood plasma. The manufacturing of plasma protein therapies (PPT) is a highly-sophisticated process that takes about seven to twelve months from plasma donation to completion of the finished product and includes donor screening, biochemical testing of each donation, plasma pooling and testing, protein purification, virus inactivation and prion removal etc. Since plasma is a biological product, rigorous testing and quality assurance occur throughout the manufacturing process[1]. The cost structure of a plasma product is therefore completely different than that of the small-molecule pharmaceuticals. Cost of collecting raw material, i.e. human plasma, can typically contribute to over 50% to the overall cost of product manufacture[2]. Whereas in small molecule pharmaceuticals, introduction of a generic version of a drug has been shown to reduce price by up to 90% relative to the brand version, manufacturer of a subsequent version of a PPT will have to make time and resource investment in clinical trials, manufacturing and post-approval safety monitoring similar to first-in-class PPT[3].

An additional complexity forms the economics of plasma fractionation as from a liter of plasma, a maximum protein output has to be achieved, while diversification of the product portfolio is essential for the business sustainability[4]. According to some analytics, if manufacturers would extract only one type of protein, their business model would be uneconomic and at least a three-product portfolio is considered as necessary for a viable operation[5].

In view of these specificities of the plasma products, it is important to take the industry perspective into consideration when assessing the value of plasma protein therapies.

[1] http://www.cslbehring.com/quality-safety/donor-to-patient.htm

[2] Charles Waller et al. Health Technology Assessment – Plasma product industry view. Pharmaceuticals Policy and Law 13 (2011)

[3] Kristina Lybecker. The Biologics Revolution in the Production of Drugs. Fraser Institute (2016)

[4] Production of plasma proteins for therapeutics use. Edited by J. Bertolini, Neil Goss, and John Curling. John Wiley & Sons, Inc. (2013)

[5] Farrugia A et al. The dynamics of contract plasma fractionation. Biologicals (2017)

PPTA reflections on the 'Proposed adaptation of the ICER value framework for the assessments of treatments for ultra-rare conditions'

While agreeing on the overall idea of a modified assessment framework, PPTA appreciates the opportunity to comment on several points of the proposal.

2.1 For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultrarare conditions against historical controls will be highlighted.

PPTA supports this clause. Since individual treatment response and non-linear pharmacokinetic behavior of PPTs complicate bivariate judgement (effective versus not effective) based on short-term observations, alternative approaches to evidence generation are needed. A methodological shift to adaptive trial designs, which allow for iterative evidence generation and a timely recognition of the drug (in)efficacy in certain subgroups has been recognized[6]. Conditional market entry schemes with post-launch evidence generation may offer a solution and are currently piloted in Europe. In view of a poor fit of the traditional drug assessment methods in rare conditions, it is important to recognize that a trade-off between the time of patient access to new drugs and the degree of evidentiary certainty will be needed.

3.1 For assessment of cost-effectiveness of a potential major advance for a serious ultra-rare condition, ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.

Constructing a cost-effectiveness model may be very challenging if based on the results of a clinical trial in ultra-rare conditions, because of insufficient knowledge of how the effect on the surrogate endpoints will translate into the effect on clinically relevant endpoints such as morbidity and mortality, in a long term. This uncertainty, multiplied by frequently seen evidentiary uncertainty shown within the clinical trial, may significantly limit the practical value of long-term cost-effectiveness modeling.

3.2 For these treatments ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from $50,000 per QALY to $500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.

As outlined in previous comment, calculating a lifetime incremental cost-effectiveness ratio may be challenging. Moreover, measuring value through a mathematic calculation of cost per QALY has several limitations. The assumed neutrality of the QALYs, i.e. no matter who benefits from

[6] Eichler et al. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. Clin Pharmacol Ther. (2015)

them, does not seem to be supported by societal preferences regarding health care resource allocation[7]. PPTA therefore encourages to put more emphasis on a structural evaluation of patient reported outcomes, 'other benefits and disadvantages' and 'contextual considerations', as outlined in 4.1.

3.3 ICER will calculate a value-based price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

Applying a higher willingness-to-pay threshold for treatments of rare conditions is a frequent international practice. In addition to the calculation of the incremental cost-effectiveness ratio (if feasible), a budget impact analysis may be important. Some ultra-rare diseases affect a limited number of people in the country, thus showing the budget impact of a drug adds a valuable perspective to the Payer information.

3.4 When ICER 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. Instead, ICER will provide a crosswalk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found.

Please, see preceding comment on the budget impact.

4.1 For report sections on "other benefits and disadvantages" and "contextual considerations," ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

This is a very important part of the assessment framework. Current assessments insufficiently involve patient perspective. When evidence is scarce or uncertain, and diseases rare and complex, effective partnerships seem essential to determine the true added value of therapies and ensure that therapies are provided at the fairest possible price[8]. Participation of patients should be considered in all phases of the project. In the recent years, there has been greater recognition for the value of patient reported outcomes (PROs). Structural use of generic and disease specific PROs in the assessment process is recommended but not consistently integrated in the policy decisions[9]. While clinicians admit to having limited expertise in handling patient perspectives[10], information from qualitative research, such as patient interviews or focus groups, can provide the

[7] Schlander M et al. Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement. J Mark Access Health Policy (2016)

[8] K.M.Facey. Patient involvement in HTA: What added value? Pharmaceuticals Policy and Law 13 (2011)

[9] http://www.eunethta.eu/outputs/endpoints-used-relative-effectiveness-assessment-health-related-quality-life-and-utility-mea

[10] Helen Chapel. HTAs and access to rare disease therapies: How can clinicians assist in the healthcare assessment of treatments for patients with primary immune deficiencies? Pharmaceuticals Policy and Law 13 (2011)

policy makers with invaluable contextual information in order to understand the burden of a rare disease and how the treatment under assessment affects the patient and the informal caregivers.

PPTA advocates for a structured integration of this information in all assessments. Recent initiatives of the English (NICE) and Scottish (SMC) Health Technology Assessment bodies, that introduced a special procedure for collecting patient and clinician perspective in (ultra-)rare diseases may serve as example.

5.1 ICER will conduct over the coming year a collaborative process through which it will seek to develop a template for providing information in its reports on the research, development, and other relevant costs related to new treatments for serious ultra-rare conditions. Until this template is completed, ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.

PPTA truly welcomes this initiative and is ready to provide input.

6.1 During public meetings of ICER's independent appraisal committees, votes on the "long-term value for money" of treatments for serious ultra-rare conditions will be done according to the same procedures for other interventions, i.e. if the base case estimate falls between $50,000$175,000 per QALY. However, for treatments of ultra-rare conditions, ICER will not assign any designation of value if the base case cost-effectiveness ratio is above $175,000 per QALY.

In view of the challenges associated with the incremental cost-effectiveness ratio calculation in rare conditions, additional considerations may be needed to provide the Payers with adequate information on the disease and the treatment. In the past ten years, many conceptual frameworks for the assessment of rare disease therapies have been developed[11]. Most of them are multicriteria decision analysis (MCDA) and include a broader range of assessment elements than traditional assessments, e.g. rarity and burden of disease, availability of treatment alternatives, level of health impact and uncertainty of effectiveness, vulnerability of patient population, manufacturing complexity etc.

PPTA encourages ICER to pay attention to these frameworks and eventually broaden the evaluation scope. In addition, next to the clinical and cost-effectiveness assessment, evaluation of ethical, organizational and societal impact of health technologies may be important[12].

Before ICER takes a position on a PPT, I would respectfully request the opportunity to collaborate with ICER either through attending a committee meeting or meeting with staff. I urge ICER not to finalize any positions that would impact patient access to plasma protein therapies without consultation with PPTA. I look forward to working with ICER as this process moves forward.

Irina Odnoletkova, PhD

Director Health Economics and Outcomes
Plasma Protein Therapeutics Association

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[11] Annemans et al. Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) Orphanet J Rare Dis. (2017)

[12] http://www.eunethta.eu/hta-core-model

Comments/Feedback on Proposed Orphan Drug Value Assessment Procedures

By

Siva Narayanan, VP & Global Head, Market Access, PTC Therapeutics, Inc.
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ICER Proposal: ICER will continue to apply the same standards of evidence for its ratings of comparative clinical effectiveness, but proposes a format in which it will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting randomized controlled trials, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit.

- **PTC Comments:** By stating upfront that 'ICER will apply same standards of evidence for its ratings…" excuses ICER from any level of accountability to consider key attributes that are unique to ultra-rare conditions concretely. Contextualizing the results based on the general evaluation/assessment criteria for evidence (which is meant for regular drugs) is not sufficient. We urge ICER to make these considerations the standard part of drug assessment in ultra-rare conditions, and this is aligned with HTA processes in place in some European countries.

ICER Proposal: ICER will continue its practice of developing a cost-effectiveness model for every new treatment; however, analyses for ultra-rare conditions will provide a broader range of cost-effectiveness threshold results, from $50,000 per quality-adjusted life year (QALY) to $500,000 per QALY. ICER will calculate a value-based price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.

- **PTC Comments:** We appreciate ICER's view on broadening the cost-effectiveness threshold results. It is a significant positive step.
    - We urge ICER to conduct relevant sensitivity analyses that not only encompasses all pertinent benefits and cost offsets associated with a new intervention, but also potential discounts and outcomes-based contracts that a manufacturer may be prepared to offer, especially in the U.S
        - ICER can solicit this info from the manufacturer as part of the deliberation process to seek additional info during the report generation process
    - Offering to 'add a wording/language on contextual considerations' is another nice gesture.
        - Sticking with the value-based price benchmark of $100K-$150K per QUALY to begin with in order to make conclusions on value, and then making allowances for contextual considerations will only dilute the initial conclusion and render un-useful. ICER may want to consider expanding the value-based price benchmark range altogether, relevant to ultra-rare conditions

ICER Proposal: For report sections on "other benefits and disadvantages" and "contextual considerations," ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

- **PTC Comments:** We again appreciate this proposal moving the assessment process in the right direction. We urge ICER to clearly state the benefits, advantages and disadvantages clearly, using a simple and explicit checklist of items to report supporting evidence.
    - For example, the economic value propositions could be stated to explicitly encompass:
        - Direct medical costs
            - Hospitalizations, ER visits, Medications
        - Non-medical costs and indirect costs
            - Time off from work, Income loss, loss of productivity
            - Impact on school attendance, presenteeism
            - Insurance premiums, Out of pocket expenses
            - Informal caregiver time, home help
            - Changes to home, vehicle, etc
            - Assistive devices/equipment
            - Travel costs
            - Social care
        - Other relevant parameters
            - Impact on community and society at large
                - Incl. opportunity costs (lost productive years and associated cost to society owing to death in the early years)
            - Quality of life impact on caregivers
- In addition, a quantitative assessment on the potential impact of delaying treatment on patient outcomes must be addressed, to give a complete picture for payers and clinicians alike
    - In such assessment, increased cost to system owing to longer use of a therapy may be reflected alongside the cost-offsets and patient benefits associated with delaying disease milestones/progression and extended survival

Other general comments for consideration:

- ICER should make it mandatory in its assessment to seek data from natural history cohorts in the concerned ultra-rare condition, if one exists, to contextualize the disease burden and the manufacturer-reported benefit of intervention (to gauge the magnitude of true benefit).
- ICER further should include in its policy a step for an 'oral hearing' during the public comment period of its draft report before it is finalized. This step is being adopted in some of the European countries.

    - Such an oral hearing may allow a manufacturer to summarize the key points concerning the report, in collaboration with Patient Advocacy Groups (representing patients) and Clinicians
- ICER should allow manufacturers to submit an updated evidence package (incl. long-term data) to enable ICER to update its report at a defined juncture (e.g., not more than once a year thereafter, following the year of initial report release)
- Some of the economic value proposition of drugs may include the societal impact and cost savings to government/public programs such as Medicaid and Medicare in the U.S. However, the same considerations may be of little to no interest to commercial payers in the U.S for various reason. ICER may want to do separate evaluations to report implications for commercial and public payers, if it is relevant to the ultra-rare condition of interest.

We share our gratitude for the opportunity to share this input.

Thank you.

Proposed Value Assessment Framework for Treatments That Represent a Potential Major Advance for Serious Ultra-Rare Conditions – Critical review

Regeneron Pharmaceuticals

Introduction

The Institute for Clinical and Economic Review (ICER) has released the document, entitled ***Proposed adaptation of the ICER value framework for the assessment of treatments for ultra-rare conditions (July 2017)***, which presents a set of adaptations to the ICER value assessment framework for treatments for ultra-rare diseases. In the present document, we report a critical review of the proposed revisions to the ICER framework, focusing on the criteria for determination of treatments representing a potential major advance for serious ultra-rare conditions, the approach to the assessment of patient outcomes, cost effectiveness and value-based pricing, and the use of R&D costs to determine an acceptable price.

Critical review and recommendations

Criteria for "potential major advance for serious ultra-rare condition"

ICER is proposing to apply the following three criteria in the definition of potential major advances for serious ultra-rare conditions:

1. "The treatment is envisaged for a US patient population of fewer than 10,000 individuals;
2. There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals;
3. The treatment potentially offers a major gain in improved quality of life and/or length of life."

We have the following comments regarding these criteria:

1. While the US government has agreed on a definition of what constitutes a rare disease (Orphan Drug Act), there is currently no corresponding definition for an ultra-rare disease. Therefore, the size of the patient population, defined as fewer than 10,000 individuals, appears arbitrary. More information providing the rationale for this threshold should be provided.

2. We disagree with the second criterion requiring "little chance of future expansion." While drug development may begin with a particular indication in mind, additional label indications may follow. It is not possible to predict whether or not a treatment will be successful (from clinical and regulatory perspectives) for the expanded population. If the indicated population is expanded, a new value assessment in the expanded population should be conducted.

3. The third criterion of "major gain in improved quality of life and/or length of life" is not defined in the proposal. Further, there is no generally accepted definition for "major gain." We propose either deleting this criterion or convening relevant stakeholders and subject matter experts to agree upon a definition.

Recommendations:

- Provide scientific rationale for the criterion requiring a patient population of fewer than 10,000 individuals.
- Remove the second criterion and re-assess the value of a therapy once additional indications have been FDA-approved.
- Remove the criterion of "major gain" or convene relevant stakeholders to provide a specific definition.

Patient outcomes

In sections 3.1 and 3.4, ICER acknowledges the uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures for ultra-rare diseases. In fact, while methodologies are available for mapping utilities and computing QALYs from standardized PRO measures (e.g., EORTC QLQ-C30, PROMIS domain measures, etc.), the collection of PROs for ultra-rare diseases can be hindered by small patient numbers, and the lack of validated instruments or methods allowing for mapping.

ICER recognizes that translating measures of patient outcomes into QALYs may not always be feasible and allows for the use of cost-consequence analyses. In this case, ICER proposes to provide a "cross-walk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found." The proposal does not clearly define a "crosswalk," nor does it specify how this crosswalk will be implemented to estimate a "cost-consequence price." The proposal also does not provide sufficient information about what is proposed by "closest clinical analogue," or what will be done if this analogue is imperfect (e.g., clinical consequences of an intervention in a specific ultra-rare disease may be different from those in another disease, treatments may not be available for the closest clinical analogue condition, or the intervention for the closest clinical analogue may be highly inefficient).

We recommend that ICER pre-specify the definition of a close clinical analogue, and if an appropriate clinical analogue cannot be identified, we recommend that ICER forego an assessment of cost consequence.

Recommendations:

- Provide more information about how the crosswalk will be applied to assess the cost-effectiveness of a given treatment.
- Pre-specify the definition of a close clinical analogue; if an appropriate clinical analogue cannot be identified, forego an assessment of cost consequence.

Threshold values

In section 3.2, ICER proposes to use a broader willingness to pay threshold range, from $50,000 per QALY to $500,000 per QALY. There is consensus in the literature about the arbitrary nature of the lower value ($50,000 per QALY), mentioning its "curious resilience" (Neumann et al. 2014). It is commonly thought to be based on the historical value of the cost of one year of dialysis. More recently, this was estimated to be $129,090 (Lee et al. 2009), and adjusted for medical care inflation, this 2009 estimate would rise to $160,000 in 2016. For the upper end of the range, opinions have ranged anywhere between three times GDP per capita, which equates to approximately $162,000 per QALY (based on 2014 numbers in the US), to just over $420,000 per QALY (Hirth et al. 2008, Braithwaite et al. 2008, Neumann et al. 2014, Marseille et al. 2015). Looking into health interventions outside of the healthcare system, the threshold may be as high as $5.6 million per QALY (Vallejo-Torres et al. 2016).

Empirical data obtained from the UK across therapeutic areas showed an enormous variation: from below £10,000 per QALY in cardiovascular disease to far above £1 million per QALY in neonatal and maternal care (Claxton et al. 2013). Thus, funding decisions alone cannot be used to inform estimation of cost effectiveness thresholds. In addition, various other methods are currently available to estimate thresholds (e.g. league tables), each with their own advantages and limitations (Birch et al. 2014, Vallejo-Torres et al. 2016, Marseille et al. 2015). Depending on the method used, different thresholds can be estimated.

Furthermore, a fixed cost per QALY threshold may not take into account all benefits observed by patients and their caregivers, and this is likely to be even more pronounced in the case of ultra-rare conditions. A wider view is required that takes into account the impact of a treatment not only on the patient, but also on the caregiver and family. The exclusion of these benefits introduces bias against conditions for which patients receive substantial care outside of the formal healthcare system (Philipson et al. 2017) and may result in a more conservative estimate or range for cost per QALY.

Despite the recommendation in section 3.2 to use a broader range for a cost-effectiveness threshold, section 3.3 states that ICER will calculate a value-based price benchmark for treatments for ultra-rare diseases "using the standard range from $100,000 to $150,000 per QALY". In addition, ICER proposes to "add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied

to decisions about other treatments." Given the broader range proposed in section 3.2 and the caveats recommended in section 3.3, it is unclear why ICER will use the standard range from $100,000-$150,000 per QALY to calculate a value-based price.

Recommendations:

- Remove the $100,000 to $150,000 cost per QALY range entirely.
- Convoke of a panel including relevant stakeholders (e.g. healthcare providers, insurers, pharmaceutical industry, academia, patients and relevant government agencies) to determine the criteria and willingness to pay values specifically for treatments for ultra-rare diseases.

The role of R&D costs in pricing

ICER is proposing to develop a template for providing information in their reports (those launching in mid-2018) on the R&D costs related to new treatments for serious ultra-rare conditions. Until then, ICER is planning to work with individual manufacturers to determine what, if any, information related to R&D costs can be shared and discussed as part of the public meetings during which ICER reports are deliberated.

We do not agree that R&D costs should be considered in ICER's determination of a value-based price.

Reported estimates of R&D costs vary widely, largely due to the differences in the methods used to estimate these costs, ranging from $160 million (Public citizen 2001, Prasad et al. 2017a,b) to $2.6 billion (DiMasi et al. 2016). For example, estimates at the lower end focus on the clinical development costs of a drug that reaches the market (Prasad et al. 2017a), while those at the higher end (DiMasi et al. 2016) include the costs associated with compounds abandoned during development, or those associated with treatments withdrawn from the market prematurely. In the broadest case, costs of failures could be amortized across the industry, and not just by the individual company. Other drivers of cost estimates previously reported include the cost of capital, the role of public subsidies to pharmaceutical companies, and the use of publicly funded research (Avorn 2015, Prasad et al. 2017a, DiMasi et al. 2016). All of this variability introduces subjectivity in the estimation of R&D costs, which may result in large differences in the reported value-based price for a given therapy.

Moreover, consideration of R&D costs for a single therapy does not take into account the value that research into a new therapeutic area or treatment might provide, even if only modest or no improvements are realized. Research furthering the understanding of a disease and therapeutic class – even if this research results in failure - has the potential to galvanize the development of a new class of treatments that may prove to be highly effective (Philipson et al. 2017). Further, using R&D costs associated with a single drug to inform value-based pricing decisions may serve as a disincentive to the pharmaceutical industry to invest in research for indications that may require a more prolonged developmental process, which may include multiple failures, or research focused on understanding a specific disease (Hughes-Wilson et al. 2012).

Recommendations:

- Inefficient drug development should not be rewarded by considering R&D costs in the value assessment and determination of a value-based price of a given therapy.
- Further, R&D costs should not be considered in ICER's value assessment and determination of a value-based price as the large variability in accounting for R&D costs will result in substantial differences in the reported value assessment and value-based price for a given therapy.

Approach for assessment: Multi Criteria Decision Analysis

For the assessment of treatments for ultra-rare conditions, ICER is proposing that the approach to rating evidence according to the ICER EBM matrix will not be modified, nor will there be different standards of evidence; instead, ICER will provide context regarding the challenges of generating evidence for these treatments. Rather than provide context, it would be preferable if ICER adopted a more systematic approach to evaluating the evidence.

In previous consultations for the general assessment framework, Multi Criteria Decision Analysis (MCDA) was rejected because it was believed that deriving quantitative weights for each individual element is not conceptually robust or practically feasible. While weighting criteria is undoubtedly challenging, this is not sufficient reason to refrain from applying this promising method. At the very least, pilot studies should be conducted to assess its feasibility; rare diseases offer an ideal context to do so.

For ultra-rare conditions, a full MCDA is even more relevant, as:

- Criteria such as "other benefits and disadvantages" and "contextual considerations" are particularly relevant for these treatments;
- There are no accepted methods for the incorporation of these benefits into the standard cost per QALY approach.

The use of a full MCDA would allow for a systematic evaluation of criteria relevant for decision making. This method has been recommended for orphan indications by the European Commission, the Office of Health Economics in the UK, and multiple health economists in the US, Canada, Europe and Russia, including the following:

- Transparent Value Framework (European Commission 2014)
- MCDA framework for orphan drugs from the Netherlands (Schey et al. 2017)
- Multi-criteria decision analysis to value orphan medicines from the UK Office of Health Economics (Sussex et al. 2013)

- Value-based reimbursement decisions for orphan drugs: a scoping review and decision framework from Canada (Paulden et al. 2015)
- EVIDEM Framework for Rare Diseases: Analysis of Issues and Policies, and Context-Specific Adaptation from Canada and USA (Wagner et al. 2016)
- Guide to core elements of value relevant to pricing and reimbursement decisions in rare diseases from Europe (Annemans et al. 2017)
- Multi-criteria decision analysis (MCDA) Approach To Ranking Rare Diseases In Russia (Fedyaeva et al. 2014).

In addition, examples of assessments of treatments currently on the market have also been published using these frameworks (Schey et al. 2017, Sussex et al. 2013).

The assessment of criteria can be executed through various methods, including value functions (Paulden et al. 2015) and simple scoring algorithms (Transparent Value Framework by the European Commission) that can be customized for individual payers. Weighting the individual criteria can be completed via methods such as Discrete Choice Experiments (Thokala et al. 2016).

Recommendations:

- ICER should adopt the recommendation of numerous governmental and non-governmental agencies and employ MCDA when evaluating other benefits and disadvantages, as well as contextual considerations associated with treatment.

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September 22, 2017

RE: "**Proposed Value Assessment Framework for Treatments That Represent a Potential Major Advance for Serious Ultra-Rare Conditions**"

Dear Dr. Pearson,

Sanofi Genzyme thanks The Institute for Clinical and Economic Review (ICER) for soliciting comment on its proposed value framework for treatments of ultra-rare conditions. We were pleased to see the proposal's recognition that the rare and ultra-rare disease context poses unique challenges with regard to patient well-being and evidence generation. Indeed, development of therapies for rare disease faces several challenges including limited information on the burden of rare disease and the benefit of treatments, lack of appropriate assessment tools, scant evidence on the natural history of the disease, difficulty generating comparative evidence due to small sample sizes, and difficulty in clinical trial recruitment due to small population sizes and high disease severity, among other issues.

However, Sanofi Genzyme has major concerns with ICER's overall approach to evaluating treatments for ultra-rare diseases. Many rare diseases still have no cure or no effective treatment, have severe impacts on health and well-being, are often life-long conditions, are associated with a higher risk of deprived care due to lack of awareness, and often affects the most vulnerable population: children.[1,2] Moreover, rare diseases often impact the patient's family and society. Given the need for continued innovation and treatment access for patients suffering from rare diseases, it is important that formal economic evaluations do not underestimate the value of the medication for the individual patient nor the alleviation of disease burden for families. Manufacturer investments in rare disease therapies are made in the face of substantial uncertainty regarding the true patient population size, the requirements around outcome measures for regulatory approval, and the safety or efficacy profile of the drug. Indeed, the 1983 Orphan Drug Act was passed in recognition of such challenges and the subsequent need for additional financial incentives to support the development of rare disease therapies.

We summarize our concerns with ICER's proposal in the following points:

- **Ultra-rare qualification criteria**: The prevalence cutoffs used by ICER lack scientific grounding and create the perception of false precision**.** ICER's limitation on growth of the treated population is not demonstrable in practice, due to substantial uncertainty inherent in rare disease.
- **Reliance on traditional health technology assessment methods**: ICER's proposal does not adequately account for evidence generation challenges inherent in rare disease, nor does it adequately incorporate widely recognized factors relevant for value assessment in rare disease, such as caregiver impacts and social preferences. Reliance on traditional technology assessment methods has hindered patient access, in other countries.
- **A clear framework is necessary**: ICER's proposal lacks clarity and commitment to robust integration of patient and societal preferences. This is particularly troubling as experience outside the US has shown that ultra-rare drug policies can have unintended consequences.

- **R&D costs for a single therapy do not accurately reflect investments**: ICER's proposed incorporation of R&D costs for a single therapy does not reflect the risk inherent in drug development, nor does it capture investments related to post-market evidence generation, which are difficult to measure in practice.

Below we provide detailed feedback on ICER's suggested framework. We look forward to working with ICER in order to ensure continued innovation and treatment access for patients suffering from rare disease.

Ultra-rare qualification criteria

Sanofi Genzyme is concerned that the qualification criteria for "ultra-rare" conditions are problematic in the context of policymaking. ICER proposes a definition of ultra-rare disease as a condition that affects <10,000 individuals, which is benchmarked to the National Institute for Health and Care Excellence (NICE), but ultimately arbitrary and lacks scientific grounding. This cutoff excludes a number of conditions that are traditionally considered at the very low spectrum of the rare disease definition, such as:

- Acute myeloid leukemia (affects about 3-5 per 100,000 in the US, or about 15,000)[5]
- Hemophilia (affects about 20,000 in the US)[5]
- Cystic fibrosis (affects about 30,000 in the US)[5]

Therapies targeted to a patient population just above 10,000, such as in the above examples, face similar challenges in terms of evidence generation as those just below the threshold. Recommendations for therapeutic access should not differ dramatically solely because the population size is right above versus right below the threshold. For example, consider two therapies: the first treats 10,000 and is found to have a base case estimate of $500,000 per quality-adjusted life-year (QALY). In such a case, the therapy will be qualified as an "ultra-rare drug" by ICER, and ICER will not vote on this therapy's "long-term value for money." The second therapy is similar to the first, except it treats 11,000 and is found to have a base case estimate of $200,000 per QALY. This second treatment will not qualify for ICER's "ultra-rare" framework, and ICER is forced to assign "low value for money." Clearly, such cutoffs create the risk of false precision when perceived by policymakers and do not rigorously incorporate other aspects of rare diseases, such as societal preferences, which can have problematic impacts on patient access to innovation based on minor differences in the treated population size.

ICER has also proposed that the potential increase in the target population be limited to 20,000, yet manufacturers cannot accurately predict whether the treated population will expand or to what extent over time. It is uncertain what subsequent indications, if any, will be pursued, and further uncertain whether pursued indications will succeed or fail. Furthermore, estimating the size of the patient population is rife with uncertainty. Knowledge about rare diseases typically increases only after the therapy is available, as diagnostic modalities and provider awareness gradually change in response to the advent of treatment. In addition, ICER does not specify a time frame, and manufacturers cannot reliably predict how labels may change beyond the immediate future.

Finally, ICER requires that therapies represent a "major gain in improved quality of life and/or length of life." Sanofi Genzyme is concerned that this criterion is vague, and there is no consensus on what constitutes a "major gain." It is likely that "major gain" will need to be assessed on a case-by-case basis for each condition. For example, in some rare diseases, such as Leber congenital amaurosis (a cause of childhood blindness) or hemophilia, novel treatments clearly have a substantial impact on patient quality of life (QoL), but the data are not necessarily available to fully quantify the impact on extending life.

Further, the limitations posed by small heterogeneous populations to data generation make evaluation and quantification of "major gains" challenging, and Sanofi Genzyme is concerned that the potential benefits

of these therapies may therefore be overlooked. For example, well-defined and appropriate endpoints may not be available, thus researchers may need to use surrogate endpoints that require validation. QoL assessments often need to be modified or newly developed for these conditions in order to capture the impacts for patients. As discussed further below, methods are still being developed to adequately capture the benefits of these therapies for patients and their families. Much of this evidence will remain unavailable or immature until the therapy has been on the market for some time, further hindering the validity of assessments made early on.

Traditional health technology assessment (HTA) methods may be infeasible or inappropriate for rare diseases

Sanofi Genzyme is concerned that ICER's application of traditional HTA methods is not appropriate in the context of rare disease. In particular, ICER proposes to utilize its standard evidence quality rating system to review evidence in ultra-rare diseases. Internationally, typical standards of evidence for HTA are often not applied to orphan drugs given frequent lack of full understanding of the diseases, challenges to conducting clinical trials, and difficulty assessing the burden of disease for small populations.[6] Through applying its typical quality of evidence system, ICER is likely to characterize the evidence as "insufficient" in the case of treatments for ultra-rare conditions due to limitations driven by small population size. However, ICER's system rates the quality of evidence without reference to a benchmark for the maximum quality of evidence achievable in a specific disease area, which is lower when treatments target very small patient populations. As a result, the system conflates poor evidence simply due to poor study design with limited evidence due to constraints driven by the population. ICER therefore needs a revised system to assess the quality of evidence for orphan drugs, given that the current system sends an unclear message in the case of rare disease.

In addition, ICER proposes to alter its cost-effectiveness analysis for ultra-rare conditions by increasing the maximum willingness to pay (WTP) threshold to $500,000 per QALY, but this threshold is not reflective of orphan drugs in practice. In a recent review of published cost-effectiveness analyses for approved ultra-orphan drugs in the EU and US, the median base case incremental cost-effectiveness ratio was $591,200/QALY, with the median estimate in the sensitivity analyses being $1,958,674/QALY.[7] Relatedly, NICE's proposed threshold of £300,000 (about $388,000) per QALY was met with serious concern from patient advocacy groups, who noted that a number of treatments for rare conditions concurrently funded by NHS England had costs per QALY above £500,000 (about $646,000).[8] Identification of an appropriate threshold is challenging, given that evidence for orphan drugs tends to be of lower quality due to challenges in generating comparative effectiveness evidence (due to recruitment issues, heterogeneity in conditions, etc.) – resulting in higher uncertainty.[9] Given this context, Sanofi Genzyme is concerned that ICER's maximum threshold will discourage patient access to much-needed therapies and, aside from cost, will not provide meaningful evaluation criteria for decision makers.

We also highlight that the limitations of formal cost-effectiveness for orphan drugs are widely recognized.[6,10] As mentioned above, the generalized QoL 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.[2] This assumption does not fully account for some populations such as children, elderly, and disabled populations, and is contrary to empirically-demonstrated societal preferences that are critical for rare diseases, such as equity or prioritization of the worst off or most urgent cases, etc.[2,11,12] Further, it is generally understood that traditional cost-effectiveness does not fully capture the value of therapies for

rare conditions, which we detail further below.[13] Thus, ICER needs to adopt methods to incorporate all aspects of value into their cost-effectiveness analyses.

Given the limitations described above, the relevance of cost-effectiveness to inform policymaking for ultra-orphan drugs is still being debated as "most ultra-orphan drugs will not meet conventional criteria for cost-effectiveness. Still, ultra-orphan drugs are often reimbursed."[14] In light of the challenges to cost-effectiveness analysis, some countries have waived formal cost-effectiveness analysis for orphan drugs. In place of formal cost-effectiveness, countries have consistently required considerations for severity of illness and lack of alternative treatment.[10] By contrast, the examples of policies in Scotland, UK, and Sweden demonstrate that the use of formal HTA analysis for orphan drugs leads to reduced coverage of these drugs, therefore impeding patient access.[10]

Comprehensive value perspectives

We applaud ICER for recognizing that rare disease can have impacts on caregivers, families, and even communities. Discussion with patient advocacy groups with experience in the condition of interest is key in understanding the patient and caregiver perspective, and we agree that these discussions will help ICER understand the burden of rare disease and value of therapy. However, discussions are only a first step in quantifying the value of reduced patient and caregiver burden. ICER's proposed text description of caregiver burden and societal impact is insufficient given that these burdens can be immense and, as demonstrated in the ICER Orphan Drug Summit, are a primary issue in the rare disease experience and patient quality of life. For example, for rare diseases such as cystic fibrosis and hemophilia, caregiver burden is substantial. Caregivers also often experience a loss of productivity (e.g. unemployment, under-employment, or avoiding more challenging/rewarding career paths).[1,15-19] In some cases, components of caregiver burden have been quantified and should therefore be included in value assessments.

Additionally, consideration of patient and caregiver preferences for outcomes is necessary for appropriate policymaking and resource allocation, and importantly, may be distinct from the considerations typically incorporated in traditional health technology assessments. For example, in Belgium, patient perspectives were incorporated through a survey fielded to the general public to understand their preferences for the reimbursement of new health interventions.[20] The study found that quality of life was given the highest priority, even over life expectancy. In response, the Belgian government now incorporates this parent/patient perspective by using corresponding weights in their reimbursement-related decision-making.[20] Thus, patient perspectives and the role of the caregiver must not be underestimated in rare disease.

Recent work has also highlighted new findings related to key components of value that are particularly relevant for rare disease, yet not included in ICER's framework, including:

Insurance value: Recent research demonstrates that, in addition to benefiting current patients, the availability of therapy provides substantial benefit to healthy individuals, who value therapy due to the risk that they may become diagnosed with disease.[21] This value to the healthy, or "insurance value" has been demonstrated to be roughly equal to the value of the therapy to those already diagnosed.[22] Value to the healthy is particularly important for rare disease, due to the severity, chronic nature, and rarity of these conditions.[13]

Value of health equity: Prior research has demonstrated that in the context of health, individuals care that treatments are distributed equitably across patients and diseases, and may be willing to tradeoff maximized population health for equitable health.[4] This value of health equity suggests that society may perceive additional value for the treatment of rare diseases in particular.

Option value: In the context of rapid innovation, patients value treatments that delay progression or mortality because these treatments may allow them to benefit from new innovation.[23] Because many treatments for rare disease are aimed at delaying disability or disease progression, it is important to

consider that incremental treatments may be instrumental for patients seeking to benefit from the next innovation.

In addition to better accounting for the patient and caregiver perspectives, ICER's framework should seek to incorporate these additional components of value and perspectives. If ICER seeks to provide a balanced perspective on the value of health technologies, assessments in the ultra-rare disease space should be made from the societal perspective, in addition to the healthcare perspective.[24] However, Sanofi Genzyme recognizes that because these perspectives are actively being developed, these values have not yet been quantified in a number of diseases. This is particularly challenging for ICER given the short timelines for reviews, and ICER's reliance on existing literature. Hence, it may be premature for ICER to conduct quantitative assessments for certain rare diseases at this time.

ICER needs a clear framework that does justice to patient and societal perspectives

Sanofi Genzyme suggests that ICER provide further clarity on their proposed approach, and we reemphasize that "getting the details right" in therapeutic assessment is critical for patients of rare disease. The proposed ICER framework relegates a number of key considerations for patients and societal value to descriptive text. Sanofi Genzyme cautions that use of descriptive text to capture these perspectives is insufficient on its own, and does not stand up to the requirements for robust and efficient decision-making.

By way of example, the Scottish Medicines Consortium introduced a new approach in 2014 with the explicit goal of increasing access to end-of-life, orphan and ultra-orphan medicines through increased approval of such drugs. The 2014 approach suggested the inclusion of patient, patient groups and clinician perspectives in the assessment of ultra-rare disease, but did not provide a clear quantitative framework to do so.[3] In 2016, the Scottish government solicited a review, which found that acceptance had not increased across all three categories as hoped.[3] Further, the review found that the perspectives of patients and clinicians did not clearly impact approval decisions and that traditional cost-effectiveness still dominated decision-making.[3] The review noted that "when considering ultra-rare disease, one size does not fit all."[3]

Similarly, NICE implemented a system for highly specialized technology for rare conditions in April 2013, which utilized a vague framework that incorporates qualitative input from the patient and caregiver as well as cost components such as value for money and budget impact. In the first 3 years under this system, NICE only provided guidance for 2 drugs "with restrictions" and in each case it took nearly 1.5 years to deliberate the decision.[25]

Incorporation of research and development (R&D) costs for a single therapy does not accurately reflect investments

Sanofi Genzyme is concerned that ICER's proposed inclusion of R&D costs for ultra-rare drugs is misleading in the context of drug pricing. The costs for drug development must be incurred by manufacturers for years before revenues for a drug are expected to accrue. In order to identify those therapies that can benefit patients and be brought to market, manufacturers invest research funding in a number of potential therapies, many of which fail. This search for effective medical innovations is funded by revenues from successfully marketed drugs, which covers the costs of both successfully launched and failed drugs. Manufacturer investment in a successfully launched drug continues well past drug launch, to support post-marketing evidence generation and safety monitoring. The R&D cost for a single drug does not reflect the risk inherent in the drug development process, nor does it reflect the need for revenues from marketed drugs to cover the costs of multiple therapies explored, only some of which are successful.[26]

Further, R&D costs only capture a subset of the total manufacturer commitment made over the lifetime of the drug. For example, requirements for post-marketing evidence generation (e.g. patient registries that

run for 10 years or longer, etc.) have become an increasingly common approach to address remaining uncertainty due to small patient populations in clinical trials. Costs associated with such post-marketing evidence generation account for a significant and increasing component of drug development, yet isolating such costs for a single therapy is rife with challenges.

We therefore feel it is inappropriate for ICER to report R&D costs in their therapeutic reviews.

Conclusion

Sanofi Genzyme appreciates ICER's recognition that unique considerations are required for rare disease. However, we feel that ICER's current proposal relies on problematic qualification criteria for "ultra-rare," which do not account for substantial uncertainty at the time of manufacturer investment and the need to support treatment advances for patients with these diseases. Further, ICER's use of traditional HTA approaches is inappropriate for rare diseases given the limitations in evidence generation, the inapplicability of QALYs to the relevant patient populations, the exclusion of societal perspectives and preferences supported by existing research, and the lack of proper accounting for the QoL impacts to those most affected by these diseases – patients and caregivers. As such, ICER's proposal may lead to inappropriate recommendations for reduced patient access to critical treatments, which, as a practice, could further disincentivize innovations for rare disease. We suggest ICER undertake substantial revision of the framework, with an emphasis on fair and balanced criteria with which to apply an alternative framework, application of lessons learned in the international context on cost-effectiveness as applied to rare disease, and meaningful incorporation of patient perspectives and broader societal values.

Yours Sincerely,

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SAREPTA
THERAPEUTICS

September 25, 2017

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: ICER's Proposed Revisions to its Value Framework for Treatments for Ultra-Rare Diseases

Dear Dr. Pearson:

Thank you for the opportunity to comment on ICER's proposed adaptations to its value assessment framework for ultra-orphan drugs. Sarepta Therapeutics is a commercial-stage biopharmaceutical company focused on the discovery and development of precision genetic medicines to treat rare neuromuscular diseases.

Sarepta appreciates ICER's acknowledgement that traditional value assessment tools do not adequately value treatments for ultra-rare conditions. Sarepta is encouraged by ICER's recognition of the challenges in generating evidence for these treatments and the importance of valuing all benefits of a particular treatment, including the potential effects on family, school, and community. We endorse the comments submitted by the Biotechnology Innovation Organization (BIO), of which Sarepta is a member. This letter supplements those comments, focusing in particular on drugs approved by the Food and Drug Administration (FDA) using the accelerated approval process.

ICER should make additional adaptations, beyond those proposed, to its value assessment framework to address the special nature of these conditions more appropriately. Below we make several recommendations for further modifications in ICER's standard framework that we believe would lead to better evaluations of ultra-rare treatments -- especially accelerated-approval products. While the limitations in ICER's current framework are most acute in the context of drugs that receive accelerated approval for ultra-rare conditions, they have broader relevance, and we hope that ultimately ICER will seek to address these limitations in its standard framework as well.

Our key recommendations can be summarized as follows:

- ICER should reframe its proposed criteria for when it would apply its modified framework, allowing for flexibility in defining a condition as "ultra-rare" and ensuring that all treatments for ultra-rare conditions are evaluated under this framework, irrespective of any potential future expansion of the treatment population.

- ICER should delay analysis of drugs approved by the FDA through the accelerated approval pathway until confirmatory studies are complete so that such treatments are not misvalued.

- ICER should incorporate input from clinical experts in a systematic, meaningful way throughout the value assessment process.

- ICER should integrate patient and caregiver preferences into its outcome measures so that the outcomes evaluated include those that patients with the relevant disease and their caregivers have identified as important.

- ICER should incorporate other benefits and disadvantages, including caregiver burden, and contextual considerations of societal value, in its cost-effectiveness calculations to ensure their importance is communicated and understood.

- ICER's procedures should provide for voting on treatments for ultra-rare conditions even if the base case cost-effectiveness ratio is above $175,000 per QALY.

These recommendations are discussed more fully below.

I. ICER Should Reframe Its Proposed Criteria for a "Potential Major Advance for a Serious Ultra-Rare Condition"

We join BIO in expressing concern over ICER's proposed 10,000-patient threshold for defining a condition as ultra-rare and advocating for a more flexible and dynamic approach that takes into account not only prevalence, but also the nature of the patient population, the severity of the disease, the speed of disease progression, and the viability of clinical endpoints establishing clinical benefit.

We also believe that ICER's proposal to limit the adapted approach to therapies with little chance of future expansion would exclude therapies that it would be appropriate to include. In most instances, it is very difficult to predict the likelihood that a particular treatment's indication will expand, let alone the future size of the treatment population. Even if such factors could be accurately predicted, it is hard to understand why ICER, having determined that treatments for ultra-rare conditions require a modified assessment process and having established such a process, would not apply this process to a treatment for an ultra-rare condition because of the possibility it might receive, in the future, an expanded indication. At the time of the value assessment, any treatment for an ultra-rare condition would face the same problems under ICER's standard value assessment framework. The possibility of a future expanded indication does not change that fact or mitigate the immediate need for assessment under a process appropriate for such treatments.

Moreover, such an approach is unnecessary. ICER has shown a willingness to update its value assessments when new evidence becomes available. For instance, ICER recently updated its value assessment for evolocumab after the release of new clinical evidence.[1] Consistent with this practice, ICER should apply the finalized adapted framework to all treatments for ultra-rare conditions and, if indications for a treatment are later expanded to encompass a non-orphan population, update the assessment using the

[1] See, "Institute for Clinical and Economic Review Posts Updated Economic Analyses for PCSK9 Inhibitor Evolocumab, Finds Less Favorable Cost-Effectiveness," available at https://icer-review.org/announcements/pcsk9-neu/.

traditional value assessment framework. Such an update likely would be appropriate in any case to reflect the new data that would be generated to support the expanded indication.

II. ICER Should Delay Analysis of Accelerated-Approval Drugs Until Confirmatory Studies Are Complete

Currently, ICER reviews new therapies shortly after FDA approval, a practice which can limit the amount of data available for review and analysis. While this timing issue is a concern generally, it is especially problematic in the case of serious ultra-rare conditions. As ICER acknowledges, the extremely small populations affected by serious ultra-rare conditions can create challenges for generating RCT-based evidence and in obtaining long-term data on safety and on the durability of clinical benefit.

These challenges are amplified for drugs that receive accelerated approval from FDA, as many drugs for serious ultra-rare conditions do, because such approval is based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity. Using surrogate endpoints can save valuable time in the drug approval process, "ensur[ing] that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies' benefits justify their risks"[2] in order to address an important unmet need. The FDA has emphasized, however, that accelerated approval requires "that the effect shown be, in the judgment of the agency, clinically meaningful, and of such importance as to outweigh the risks of treatment. This judgment does not represent either a "lower standard" or one inconsistent with section 505(d) of the act, but rather an assessment about whether different types of data show that the same statutory standard has been met."[3] In order to confirm the anticipated clinical benefit, a drug's manufacturer may be required to conduct additional "post-market" studies, known as phase 4 confirmatory trials, which provide further information but only after some time has passed.

We recommend that ICER delay conducting value analysis on any drug approved through the accelerated approval process until its manufacturer conducts phase 4 confirmatory trials that directly and definitely characterize the clinical benefit. ICER's proposal states: "[T]he available evidence [for orphan drugs] often provides less certainty in comparative clinical effectiveness. There is therefore a heightened sense that for many orphan drugs, especially those approved on accelerated pathways, additional evidence generation after regulatory approval will be needed to gain additional certainty regarding the benefits and harms among various subpopulations."[4] We think the appropriate response to this concern is to forebear performing a value assessment until information from confirmatory trials is available that will permit a more accurate assessment. Proceeding too soon could have the effect of inappropriately limiting patients' access to life-saving medications.

III. ICER Should Incorporate Input from Clinical Experts in a Systematic, Meaningful Way

As discussed more fully below, accurately valuing care requires that ICER identify and evaluate the outcomes that are most relevant and meaningful to patients and their families, as well as the real world

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[2] FDA, "Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics" at 1 (May 2014) (emphasis added).

[3] FDA, "New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval," 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992). (emphasis added)

[4] "Assessing the Effectiveness and Value of Drugs for Rare Conditions," May 2017, at 14.

impact of therapy. Directly involving clinical experts in all aspects of ICER's analysis is critical to ensuring that treatments are evaluated in ways that are relevant to and consistent with clinical practice. ICER should ensure that the perspectives of patients' providers are represented throughout the process, including scoping projects and vetting the clinical effectiveness questions and model inputs, and that they sit on the health technology assessment panels, public advisory councils, and independent appraisal committees.

Only clinical experts in these chronic, complex rare diseases can be expected to understand the evolution of the standard of care, the nuances in individualized clinical decision-making, and the impact of therapy on the disease. Clinical experts without direct experience with patients and their families will not be able to provide the same in-depth knowledge of these conditions and their treatments. The active involvement of clinical experts in every part of this process is essential to accurate and comprehensive valuation of treatments.

IV. ICER Should Integrate Patient and Caregiver Preferences into its Outcome Measurements

We appreciate ICER's recognition that patient perspectives on the value of interventions should be reflected in its value framework. With patient-centricity fueling innovation in rare disease research and drug development, it is critical that patient perspectives on value and preferences (as well as caregiver preferences for pediatric and certain other patient populations where patients are not in a position to make decisions about their care) are incorporated into value assessments. Especially in the case of chronic, complex conditions affecting small patient populations, patients and their caregivers can offer expertise on their conditions that is otherwise not available, both from their perspective as patients, but also through their close collaborative relationship with the medical community. The outcomes evaluated by a value-of-care model must include those that patients with the relevant disease have identified as important and consistent with their treatment goals. Unfortunately, while the full text of an ICER report may include a narrative discussion of patient and clinician perspectives, users continue to rely on quality adjusted life year (QALY) measurements that do not incorporate preference data from people who have the disease in question.

In addition to involving patients and their caregivers in ICER's evaluation process, ICER should recognize the value of patient data and expand the sources and types of data it relies upon. While RCTs provide strong assurance of validity, too often they do so at the expense of important insights on how treatments fair in actual clinical settings and the value of those treatments for patients. Data from real-world settings and directly reported by patients offer important complements to traditional trial data, which is why the FDA Reauthorization Act of 2017[5] and the 21st Century Cures Act[6] require FDA to explore ways to incorporate patient experience data and real-world evidence (RWE) into its regulatory framework.

Fortunately, patient engagement science and related tools, such as patient and clinical data registries, are developing rapidly and ICER can give them a material role in its assessments. For instance, Parent Project Muscular Dystrophy (PPMD), an advocacy group, has completed multiple patient preference studies that use scientifically validated preference methods to measure patient and caregiver preferences and produce quantitative evidence as to their views on potential benefits and risks of candidate therapies

[5] Pub. L. 115-52. This law is informally known as "PDUFA VI."

[6] Pub. L. 114-255, sec. 3022.

and on benefit/risk trade-offs.[7] PPMD has partnered with social scientists and health economists from Johns Hopkins University to develop a survey instrument that used the best-worst scaling (BWS) method to measure respondents' views.[8] Additionally, a UCLA study used patient-entered data within PPMD's DuchenneConnect registry and found that the data could be used to assess therapeutic benefits and evaluate comparative effectiveness of steroid therapy in patients.[9] Such real-world patient data is increasingly available for many other disease states through sources such as electronic health records, payer claims data, new technologies for patient generated data, and dedicated registries.[10] When patient data is not available relative to a particular disease, ICER should survey patients at various stages of the disease's progression and spectrum so that information about patient preferences related to quality-of-life improvements or declines and other aspects of value can be incorporated in its analysis.

V. ICER Should Incorporate Other Benefits and Disadvantages, Including Caregiver Burden, and Contextual Considerations of Societal Value, in its Cost-Effectiveness Calculations to Ensure Their Importance is Communicated and Understood

Under ICER's current procedures, its cost-effectiveness metric -- the QALY -- does not adequately capture the comprehensive value a therapy offers to individual patients, the health care system, and society. QALYs do not holistically assess the value of the therapy to the individual patient, families, and the larger community. For several reasons, the limitations of ICER's current cost-per-QALY paradigm are especially apparent in evaluating treatments for serious ultra-rare diseases and should be addressed first in the context of those diseases.

We appreciate that ICER is attempting to take limitations on the availability of certain types of data into account by highlighting this issue in its report; however, we are concerned that this approach does not give these considerations the same importance as those considerations that ICER quantifies and that affect its "bottom line" conclusions. Consequently these "contextual," non-quantified considerations may have a minimal effect on decision-making. Moreover, ICER says only that it will consider "in its own judgments," whether to highlight specific context regarding these challenges, providing no assurances that the reasons for limitations on data at the time of FDA approval will be considered at all. As a consequence, decisions by payors and policymakers about coverage and payment for drugs with critically important "contextual" considerations may be unfairly biased against these innovative, life-saving treatments, limiting access for

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[7] See, e.g., Timothy R. Franson, MD and Holly Peay, MS, CGS, "Benefit-Risk Assessments in Rare Disorders: The Case for Therapeutic Development in Duchenne Muscular Dystrophy as the Prototype for New Approaches," available at http://www.parentprojectmd.org/site/DocServer/br_paper_v11__2_.pdf;jsessionid=2C381495CB3753608053FD8DD624B686.app247d?docID=14503.

[8] See, Ilene L. Hollin *et al.,* "Patient-centered Benefit-Risk Assessment in Duchenne Muscular Dystrophy," Muscle Nerve 55: 626–634 (2017), available at http://onlinelibrary.wiley.com/doi/10.1002/mus.25411/abstract; Ilene L. Hollin *et al.,* "Caregiver Preferences for Emerging Duchenne Muscular Dystrophy Treatments: A Comparison of West-Worst Scaling and Conjoint Analysis," J.F.P Patient (2015) 8:19, available at http://www.parentprojectmd.org/site/DocServer/Hollin_Patient_2014.pdf?docID=15744; Holly L. Paey *et al.,* "A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy," Clinical Therapeutics 36: 624-637 (2014), available at http://www.sciencedirect.com/science/article/pii/S0149291814002094.

[9] Richard T. Wang *et al*., "Online Self-Report Data for Duchenne Muscular Dystrophy Confirms Natural History and Can be Used to Assess for Therapeutic Benefits," PLoS Curr. 2014;6, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4207635/.

[10] For instance, NIH's website includes a non-exhaustive list of over 50 disease registries. https://www.nih.gov/health-information/nih-clinical-research-trials-you/list-registries.

patients, discouraging R&D investment in treatments for rare diseases, and undermining the policies Congress and the FDA have put in place to address important unmet medical needs.

A. ICER Should Incorporate Caregiver Burdens in Cost-Effectiveness Calculations

Caregiver and family burden for serious health conditions can be significant and must be incorporated into value analyses. Many diseases, particularly those that are profoundly disabling to the patient for long periods of time, carry immense indirect costs related to the burden on caregivers. We appreciate that one of the "other benefits and disadvantages" that ICER explicitly considers in its reports is whether "the intervention will significantly reduce caregiver or broader family burden."[11] We also appreciate that, in the report sections on "other benefits and disadvantages" and "contextual considerations," ICER proposes to include a broader frame to seek evidence and perspective on the potential for treatments for ultra-rare conditions to affect positively the family, school, and community.[12]

These domains are critically important not just for ultra-rare conditions but in assessment of medical treatments more broadly. As ICER has acknowledged, "the explicit consideration of other benefits and disadvantages and contextual considerations should be a core element of ICER reports and of the deliberation on value at public hearings;"[13] yet ICER does not integrate "other benefits and disadvantages" and "contextual considerations" into its quantitative assessments. Members of the appraisal committees will vote "yes", "no" or "uncertain" as to whether particular benefits, disadvantages or other considerations apply, but, as we understand it, these votes will have no effect on assigned cost-effectiveness thresholds or value-based pricing benchmarks. Unless these "other benefits and disadvantages" and "contextual" considerations are reflected in ICER's quantitative analysis, we are concerned they will not meaningfully affect coverage and payment decisions by payors and policymakers.

Therapies that can slow disease progression and improve quality of life for families and caregivers have important benefits that should be fully considered and integrated into the quantitative aspects of the value assessment. Many aspects of caregiver burden can be quantified in economic terms as they have a quantifiable opportunity cost. While there are still significant knowledge gaps in the areas of health economics and caregiver burden, especially for rare and ultra-rare diseases, this is a rapidly evolving and important area of qualitative and quantitative research. For instance, in a burden of disease study of Duchenne muscular dystrophy published in the Journal of American Academy of Neurology, researchers looked at certain limited aspects of this burden and found that the mean annual household burden was $75,820, the mean informal caregiver burden was $13,370, and the mean indirect costs were $45,080.[14] To the extent data on caregiver burden is available, ICER should incorporate these costs (or cost savings) into its economic models to assess the impact of caregiver burden on a drug's cost-effectiveness.

B. ICER Should Reflect the Societal Value Placed on Helping People With Rare, Severe Diseases and Limited Treatment Options in Cost-Effectiveness Calculations

Another key limitation in ICER's approach to measuring cost-effectiveness -- which is especially problematic in the rare disease context -- is the failure to take a societal perspective. As ICER observed,

[11] "Overview of the ICER Value Assessment Framework and Update for 2017-2019," p. 21.

[12] "Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions," Section 4.1.

[13] "Overview of the ICER Value Assessment Framework and Update for 2017-2019," p. 19.

[14] Erik Landfeldt *et al*., "The burden of Duchenne muscular dystrophy," Neurology 2014;83:529-536.

"discussion at the Orphan Drug stakeholder meeting suggested that a combination of complementary factors, specifically high severity and the potential for a substantial gain in quality and/or length of life, would create a situation in which special attention to broader ethical and contextual issues should accompany any traditional analysis of cost-effectiveness and potential budget impact."[15] ICER's proposed adaptions to its standard value assessment framework do not address these issues adequately, as they are not integrated into the "bottom line" cost-effectiveness analysis. As the National Pharmaceutical Council has observed, ICER's updated framework still "uses a health system or payor perspective," whereas NPC recommends value assessments "not only from a health system perspective but also from a societal perspective," as "[a]ssessments from a health system perspective narrow the value that innovative therapies appear to bring to patients," whereas a societal perspective provides a "more encompassing view and a broader understanding of treatment value."[16]

Integrating a broader societal perspective into cost-effectiveness analyses has important advantages over considering these issues "contextually," and it is challenging but doable -- a subject of considerable attention and exploration. These points are illustrated well by a recent article on QALYs as a measure of value for cancer treatments:

> HTA [health technology assessment] bodies such as NICE currently rely on a deliberative process to weigh up quantitative evidence on cost per QALY alongside other considerations they deem relevant. Deliberative processes are argued to have some important advantages in HTA, allowing decision makers to be flexible and to exercise ad hoc judgements as they consider appropriate. However, a problem with this approach is that the importance that decision makers assign to these different aspects of benefit is not transparent. This risks a lack of consistency between decisions over time …. <u>It potentially reduces accountability to stakeholders …and fails to give clear signals to the life sciences industry about (a) what is considered to be of value to the health care system and therefore (b) where they should prioritise research and development (R&D) effort.</u> … It is clear that considerations other than QALYs are being taken into account in HTA but not how much importance is placed on these other considerations.
>
> There are a variety of means by which these other aspects of value might be taken into account in a more systematic way alongside QALYs:
>
> – QALYs could be 'weighted' to reflect any differences in value society places on QALY gains by some patients/diseases, where that is supported by evidence regarding social preferences;

[15] "Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-Rare Conditions" at 4.

[16] "Appropriate Value Entails a Broad Perspective of Impact and a Comprehensive Use of Evidence", Robert W. Dubois, NPC Chief Science Officer and Executive Vice President, Sept. 12, 2017.

- Both QALYs and other aspects of benefit from cancer medicines could be monetised, using willingness to pay studies, and monetary measures of benefit weighed up alongside costs, using cost benefit analysis;

- QALYs gained could be considered alongside other, quantified aspects of benefit, and combined in a way that reflects the trade-offs people are willing to make between them and then an aggregate measure of benefit is considered alongside cost. There is a set of methods available to facilitate this, known as multiple criteria decision analysis (MCDA).[17]

Importantly, integrating a broader social perspective into its cost-effectiveness analyses instead of taking a more narrow payer perspective on cost-effectiveness would accord with ICER's mission as a trusted non-profit organization that "seeks to play a pivotal role in creating a future in which collaborative effects to move evidence into action provide a foundation for a more effective, efficient, and just health system"[18] and that "do[es] not represent the interests of the insurance industry."[19] With that mission, performing cost-effectiveness analyses that reflect a broader societal perspective would be appropriate and expected. We understand this would present challenges, but it is an important endeavor that is most crucial in the area of orphan drugs and could start with these therapies.

VI. ICER's Procedures Should Provide for Voting on Treatments Even If the Base Case Cost-Effectiveness Ratio is Above $175,000 per QALY

ICER proposes that independent appraisal committees' votes on the "long-term value for money" of treatments for serious ultra-rare conditions generally will follow the same procedures used for other conditions.[20] However, "given the broader considerations and possible distinctive weightings for other benefits and for contextual considerations related to treatments for serious ultra-rare conditions," ICER proposes that it will not assign any value rating to ultra-rare treatments if the base-case cost-effectiveness ratio exceeds $175,000 per QALY. ICER believes that it will be more informative to capture the votes on other benefits and contextual considerations, highlight how these factors often play an augmented role in value determinations for treatments of ultra-rare conditions, and allow decision-makers to consider this information without an ICER-designated value rating.

We doubt that not assigning a value will have the intended effect of focusing payors and policymakers on other benefits and contextual considerations. Decision-makers will know that generally treatments with a cost-effectiveness ratio exceeding $175,000 per QALY are considered low value by ICER

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[17] NJ Devlin and PK Lorgelly, "QALY as a measure of value in cancer," Journal of Cancer Policy, 11 (2017) 19-25, 22-23 (emphasis added) (internal citations omitted).

[18] http://icer-review.org/about/.

[19] ICER website, "What is ICER?"

[20] As part of ICER's 2017-2019 update to its overall value assessment framework, ICER decided that independent appraisal committees would only vote on the "long-term value for money" of a treatment if the base case cost-effectiveness ratio fell between $50,000 and $175,000 per QALY. Otherwise, treatments with a cost-effectiveness under $50,000 per QALY would automatically be determined to be of "high" long-term value, whereas treatments above $175,000 per QALY would be designated as "low" long-term value.

and are likely to infer that the treatment has a “low value” despite the lack of formal categorization by ICER. We believe a better approach -- in addition to expanding the cost-effectiveness metrics as discussed above in section V -- would be for independent appraisal committees to vote on the “long-term value for money” of treatments for ultra-rare diseases with a cost-effectiveness ratio exceeding $175,000 per QALY. Those committees can then consider any other benefits and contextual considerations that ICER has not been able to quantify in determining the value to be low, intermediate or high. Payors and policymakers would still be able to incorporate their own judgments regarding those other considerations in their ultimate decisions regarding coverage and payment for a treatment but would have the advantage of this additional guidance.

* * *

Thank you for your attention to this letter. Sarepta hopes our comments will be useful and would welcome the opportunity to provide any further information you might find helpful. Please feel free to contact Diane Berry at dberry@sarepta.com or 617-274-4000 if you have any questions about these comments or if we can be of further assistance.

Sincerely,

Douglas S. Ingram
President & CEO

September 25, 2017

VIA ELECTRONIC DELIVERY

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

Re: Proposed Adaptation of ICER Value Framework for the Assessment of Treatments for Ultra-rare Conditions

Dear Dr. Pearson:

Spark Therapeutics ("Spark") is pleased to submit these comments regarding the Institute for Clinical and Economic Review's (ICER) "Proposed Adaptation of ICER Value Framework for the Assessment of Treatments for Ultra-rare Conditions" ("Proposed Adaptation"). We appreciate ICER's efforts to adapt its framework to acknowledge the complex issues surrounding informed decision-making relating to ultra-rare disease (URD) therapies. We remain highly concerned, however, about the ability of uniform cost-effectiveness analysis frameworks to accurately and comprehensively value life-changing therapeutic options for patients with URDs. These comments focus on the challenges that the binary nature of the framework presents for encouraging innovation; the lack of justifications for adjustments to value thresholds; and the negative effects posed on considering higher incremental cost-per-quality-adjusted life year (QALY) thresholds when the same value-based-price benchmarks and thresholds are used for determining long-term value for money.

About Spark Therapeutics

Founded in March 2013, Spark is a late clinical-stage publicly traded gene therapy company. Its investigational therapies have the potential to provide long-lasting effects, dramatically and positively changing the lives of patients with conditions where no, or only palliative or prophylactic, pharmacological therapies exist. Greater understanding of the human genome and genetic abnormalities has allowed our scientists to develop investigational therapies that target very specific genetic diseases. This approach holds great promise for the realization of effective treatments to a host of inherited diseases, including the devastating orphan diseases that are the focus of our current efforts.

As ICER is aware, our most advanced product candidate is being studied to treat a rare inherited retinal disease (IRD) caused by biallelic *RPE65* gene mutations. Our pipeline also contains gene therapy candidates targeting other ophthalmic conditions, as well as liver-associated diseases such as hemophilia and fatal, neurodegenerative disorders such as Huntington's disease. Spark is committed to helping to ensure access to these potentially transformative treatments to the right patients at the right time.

Current evaluations using adapted framework for ultra-rare conditions

ICER is proceeding with an assessment of voretigene neparvovec (VN) under an adapted framework. From a procedural standpoint, we believe ICER should not have undertaken the review of VN under a framework that is not yet finalized. It is difficult to anticipate how an evaluation will progress under a framework that is still subject to public comment and further revision.

Spark encourages ICER to adhere to procedural protocols and timelines in the future to ensure that frameworks and adaptations to frameworks are final prior to use for particular assessments. Requesting public comment in scoping documents on use of a modified framework that is not yet finalized denies stakeholders a meaningful opportunity to comment on whether the framework is appropriate for the specific treatments under review.

Summary of Spark's comments

Spark appreciates ICER's recognition of the complex challenges in defining policy to inform decision-making on access to therapies for ultra-rare diseases (URDs). Upon review of the proposed ICER framework, four main concerns arise from the current proposal:

- The binary nature of the application of the adapted framework (i.e., on the basis of whether a therapy is intended for a URD population or not), which conflicts with prevailing legislation and policy for encouraging innovation in health care.
    - See response to Section 1.1 below.
- Adjustments to value thresholds (e.g., willingness-to-pay range, value-based-price benchmarks, incremental cost-per-QALY thresholds for long-term value-for-money determinations) lack scientific, social, or policy justification, omitting, for example, consideration of available evidence on socially optimal allocation of healthcare expenditure.
    - See responses to Section 3.3 below.
- Spark appreciates ICER's proposal to adopt a "broader frame" in its consideration of "other benefits and disadvantages". There is strong correlation between rarity and unmet need[1], and therefore a heightened need to account for these benefits and disadvantaged in URD population. However, we are concerned that there is often limited quantitative evidence available relating to the direct and indirect benefits and costs in URD populations, which may yield a systematic bias against appropriately incorporating these benefits and disadvantages in URD populations.
    - See response to Section 4.1 below.
- The use of the same value-based-price benchmarks ($100,000 - $150,000 / QALY) and thresholds for determination of long-term value for money ($50,000 - $175,000 / QALY) effectively negates the impact of considering higher incremental cost-per-QALY thresholds in cost-effectiveness analysis.
    - See response to Section 6.1 below.

[1] Rodriguez-Monguio R, et al. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? 2017. Orphanet Journal of Rare Diseases;12:1.
Groft SC. Rare Diseases Research Expanding Collaborative Translational Research Opportunities. Chest. 2013 Jul; 144(1): 16–23.
Medic G, et al. Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe. J Mark Access Health Policy. 2017; 5(1): 1299665.

To determine the adaptations to ICER's framework necessary to meet the Institute's broader purpose, it is worthwhile to consider that purpose explicitly. Per ICER's general value assessment framework:

> *"Ultimately, the purpose of the value framework is to form the backbone of rigorous, transparent evidence reports that, within a broader mechanism of stakeholder and public engagement, will* ***help the United States evolve toward a health care system that provides sustainable access to high-value care for all patients****.*
>
> *In this effort ICER is guided by several key underlying principles. One is that we act with respect for all, in concordance with a presumption of good will on the part of all participants and stakeholders in the health care system.* ***ICER does not intend to target any particular interest group or organization. There are many areas in which the US health system fails to serve patients well, in which access to care is suboptimal, waste and inefficiency pose major problems, and costs to patients and the health system fail to align with added value.*** *ICER believes that only through collaborative efforts, built upon a foundation of civil discourse and honest consideration of evidence on effectiveness and value, can lasting progress be made on behalf of patients today and those of the future.*
>
> *….*
>
> ***ICER's value assessment framework seeks to place scientific methods of evidence analysis at the heart of a clearer and more transparent process.*** *The value framework reflects our strong underlying belief that rigorous thinking about evidence can prevent the kind of waste that strains our ability to provide patient-centered care. The framework also is intended to support discussions about the best way to align prices for health services with their true added value for patients. While considering value and linking it to pricing and insurance coverage cannot solve every dilemma, nor satisfy every need, ICER believes it offers the best hope of avoiding rationing of care by the ability of patients to pay for care, and that it can promote a more dynamic, innovative health care system that will make the best use of available resources in caring for all patients."*[2]

The stated purpose of ICER's value assessment framework, to create a scientifically-informed mechanism that will generate sustainable access to high-value care without targeting particular interest groups or organizations, should inform the adaptations made to create a fit-for-purpose framework for URDs.

Per Section 3.1 of the proposed adapted framework for URDs, it is proposed that cost-effectiveness analysis will continue to be used as a significant basis for ICER's evaluations. In order to comply with its purpose, ICER therefore must consider the implications on particular patient groups, as well as the scientific evidence surrounding the socially efficient use of cost-effectiveness analysis in recommendations regarding allocation of healthcare expenditure.

For instance, it has been observed that cost-effectiveness analysis inherently discriminates against the elderly and the disabled.[3] Such implications of ICER's analysis must be addressed, particularly in the context of URDs, which are often chronic diseases (i.e., involving a degree of chronic/long-term disability, which may persist in spite of treatment of certain symptoms and complications) with a genetic etiology. Failure to do so would target particular interest groups, namely patients with URDs and their caregivers, conflicting with ICER's statement of purpose. Applying the same value-based-price benchmarks and thresholds for determination of long-term value for money for general medical technologies and ultra-orphan drugs (UODs), in order to guide decision making affecting patient access, gives rise in practice to such discrimination.

[2] ICER, Overview of the ICER value assessment framework and update for 2017 – 2019 p. 3 – 4 (2017) (emphasis added).
[3] Neumann et al. Legislating against Use of Cost-Effectiveness Information. 2010. N Engl J Med; 363:1495-1497.

In addition, ICER's adapted framework should be informed by more systematic appraisal of evidence regarding the socially efficient use of cost-effectiveness analysis in recommendations regarding allocation of healthcare expenditure. In Section 1.2, ICER states, "Ethicists and others have argued, however, that rarity alone does not justify an alternative approach to value assessment."[4] This statement, however, does not clearly reflect research on the societal preferences; there is strong correlation between rarity and unmet need[5], and studies of societal preferences consistently find a preference for prioritizing diseases with severe unmet need.[6] As such, although in the abstract, rarity alone may not drive social preferences - i.e., all else being equal between two patients, society may not prefer to treat the patient with the rarer disease - in practice, all else is not equal (in particular, unmet need), indicating a disconnect between ICER's stated perspective on rarity and the realities of clinical practice.

While societal preferences for allocation of healthcare expenditure may seem difficult topics to account for in ICER's proposed evaluation framework, many of the most prominent users of such frameworks have recently taken steps to do so. As examples, in both England and the Netherlands, the health-technology assessment bodies (NICE and Zorginstituut Nederland (ZiN)) have taken steps to weight QALY gains by adjusting cost-per-QALY threshold for magnitude of incremental QALY gains (generally reflective of the severity of the disease and the lack of alternative treatment/unmet need) and for disease severity, respectively.[7] NICE's proposed approach to QALY weighting for URDs (as part of its "highly specialised technologies" process) involves use of an incremental cost-per-QALY threshold ranging from 5 to 10 times the standard level[8], depending on factors such as the severity of the disease and the lack of alternative treatment/unmet need.[9] Applying such adjustments to ICER's standard thresholds, for example value-based-price benchmarks of $100,000 - $150,000, would suggest use of a range of $500,000 - $1,500,000

[4] The basis for this statement appears to be a panel discussion held in May 2017 that was organized by ICER, as opposed to a systematic review of existing research.

[5] Rodriguez-Monguio R, et al. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? 2017. Orphanet Journal of Rare Diseases;12:1.
Groft SC. Rare Diseases Research Expanding Collaborative Translational Research Opportunities. Chest. 2013 Jul; 144(1): 16–23.
Medic G, et al. Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe. J Mark Access Health Policy. 2017; 5(1): 1299665.

[6] Drummond MF, Towse AK. Orphan drugs policies: a suitable case for treatment. Eur J Health Econ. 2014;15:335-40.
Ubel PA. Pricing life - why it's time for healthcare rationing. Cambridge, MA: The MIT Press; 2000.
Richardson J, Sinha K, Iezzi A, Maxwell A. Maximising health versus sharing: measuring preferences for the allocation of the health budget. Soc Sci Med. 2012;75(8):1351-61.
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Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22(8):948-64.

[7] Raftery J. NICE's proposed new QALY modifier for appraising highly specialised technologies The BMJ Opinion2017 [updated 18 April 2017]. Available from: http://blogs.bmj.com/bmj/2017/04/18/nices-proposed-new-qaly-modifier-for-appraising-highly-specialised-technologies/.
National Institute for Health and Care Excellence. NICE gets go-ahead to fast-track more drug approvals NICE2017 [updated 15 March 2017]. Available from: https://www.nice.org.uk/news/article/nice-gets-go-ahead-to-fast-track-more-drug-approvals.
Zwaap J, Knies S, van der Meijden C, Staal P, van der Heiden L. Cost-effectiveness in practice. Zorginstituut Nederlands; 2015 26 June 2015.

[8] In the UK, NICE uses an incremental cost-per-QALY threshold range of £20,000 - £30,000 in standard technology appraisal. It has proposed that HSTs with cost/QALY ≤ £100,000 (5 times the lower bound of the standard range) would receive coverage, and that for those with cost/QALY > £100,000, the threshold would be £10,000 x the incremental QALYs up to a maximum threshold of £300,000 (10 times the upper bound of the standard range).

[9] These factors are common drivers of large incremental QALY gains.

in the adapted framework for URDs. ICER does not offer analysis or any explanation for why its value-based-price benchmarks and thresholds are considerably lower than those used by NICE in England.

While challenges persist around how to implement QALY weights and how to identify and set the appropriate willingness to pay for URD products, NICE and ZiN's initial efforts represent steps in the right direction to optimize societal efficiency of allocation of healthcare expenditure, based on available evidence. However, a common critique of NICE and ZiN's approaches remains that the proposed thresholds continue to lack justification/scientific basis [10] (e.g., underscored by the fact that it is impossible, using the annual discount rate of 3.5% on lifetime benefits recommended by NICE, to reach the upper threshold[11]). ICER's adapted threshold for URDs should improve upon these efforts, by more transparently incorporating societal preferences for allocation of healthcare spending in cost-effectiveness analysis based on scientific, empirical research.

Conclusion

ICER proposes a process for assessing drugs for URDs (i.e., ultra-orphan drugs or UODs) that in practice will be very similar to the framework used to assess all other therapies, citing but ultimately failing to meaningfully incorporate research on and observed practice of how other bodies assess the long-term value of UODs. ICER did not conduct systematic literature reviews of research assessing the available evidence to inform the adapted framework; instead, its approach is ultimately justified on select research, and a panel held in May 2017 in which selected researchers in the field were invited to contribute.

ICER should conduct systematic literature reviews to identify societal preferences relevant for informing UOD value assessment in the United States, allowing it to implement in a more informed and scientifically justified manner higher willingness-to-pay thresholds for UODs recently adopted by international bodies, and assess budget impact first in its reporting. The approach that ICER outlines in the adopted framework for assessing UOD value may inherently discriminate against patients with ultra-rare, genetic disorders.

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[10] NICE. Consultation on changes to technology appraisals and highly specialised technologies- Analysis of responses to the consultation (Question 10). February, 2017. Available at: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/TA-HST-consultation-report.pdf
Nuijten MJC, Dubois DJ. Cost-Utility Analysis: Current Methodological Issues and Future Perspectives. Front Pharmacol. 2011; 2: 29. doi: 10.3389/fphar.2011. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3113167/pdf/fphar-02-00029.pdf

[11] At a discount rate of 3.5%, it is a mathematical impossibility for a treatment to demonstrate the 30 incremental QALYs that would result in the maximum threshold of £300,000/QALY being applied, even if assuming (a) immediate death at birth for patients treated with the comparator and (b) perfect health throughout life (health utility of 1.00 per year) for patients treated with the intervention. This can be seen from the fact that a patient experiencing immediate death at birth has 0 lifetime discounted QALYs and (b) the series of discounted QALYs for a person living in perfect health throughout life is a geometric series. Applying the formula for the sum of a geometric series, where 'a' = value of a year at perfect health = 1, and 'r' = 1/(1+discount rate):

- Sum of 'n' observation ('Sn') = a + ar + ar^2 + ... + ar^(n-1)
- Multiplying both sides by r: rSn = ar + ar^2 +... + ar^(n-1) + ar^n
- Subtracting the second line from the first and factoring: Sn* (1-r) = a * (1-r^n)
- Therefore: Sn = a * (1-r^n) / (1-r)

For discount rate = 3.5% and arbitrarily high n, the series converges (in the limit) to 29.57, and reaches only 28.6 at 100 years of perfect health (i.e., assuming 100% of people on treatment live to 100 years of age).

Spark's detailed responses to specific sections of ICER's proposed adapted framework are set forth below:

Section 1.1 from Proposed ICER Framework

ICER will consider using an adapted approach to value assessment for treatments that will be called a "potential major advance for a serious ultra-rare condition" if the three following criteria apply:

- **The treatment is envisaged for a patient population of fewer than 10,000 individuals**
- **There is little chance of future expansion of indication or population that would extend the size of the treated population above 20,000 individuals**
- **The treatment offers a major gain in improved quality of life and/or length of life**

Spark Response

Spark is encouraged by ICER's attempt to adapt its assessment framework to recognize rarity and the magnitude of health benefits associated with drugs to treat URDs. However, the proposed criteria for consideration under the adapted framework raise concerns about how these criteria have been developed and how they will be implemented. Specifically:

- The absolute size (i.e., 10,000) of patient populations meeting ICER's criteria appears at odds with consensus reached in the literature and prevailing legislation;
- The selection of a fixed threshold appears arbitrary, given evidence suggesting that the impact of small patient populations on commercial viability is continuous in the population size; and
- In practice, particularly when evidence is limited as is common for URDs, accuracy and consistency of application of the "major gain in improved quality of life and/or length of life" criterion may be challenging.

These points are explained further below.

ICER notes:

> *"ICER believes that application of adapted methods of value assessment are not needed for the majority of 'orphan' drugs as defined by the Orphan Drug Act, as sufficient patient numbers are usually available for 'routine'" clinical trials, and outcome measures are likely to be relatively standardized and well-documented. Only when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation. A patient population of 10,000 equates to approximately three patients per 100,000 overall population in the United States."*

It is unclear on what basis ICER concludes that, "[o]nly when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way to recognize the distinctive practical challenges to evidence generation, and to give special consideration to value in the context of the price X volume needed to provide adequate rewards for risk and innovation." Both published evidence and prevailing legislation suggest that challenges to the commercial viability of research and development of products for rare diseases are not limited to diseases with patient population below ICER's 10,000 ceiling (i.e., such challenges continue to be encountered for rare conditions with patient population larger than ICER's 10,000 ceiling). Drummond et al. (2007)[12] observe that, "[p]atients with rare diseases have historically been underserved by commercial drug development. Over time, a consensus has emerged in many countries or regions to address this disparity by means of specific legislation for drugs to treat rare diseases (usually called 'orphan drugs'). In several

[12] Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007 Winter;23(1):36-42.

regions, orphan drug legislation has been enacted, which has successfully encouraged the development of drugs that, in the absence of such interventions, would not be commercially viable." As noted by Drummond et al., challenges in commercial drug development are not limited to URD products, as evidenced by the fact that the Orphan Drug Act (1983) aims to facilitate drug development for diseases affecting 200,000 patients or fewer, a level 20 times ICER's proposed threshold. Further, it should be noted that since the threshold of 200,000 was specified in the enactment of the Orphan Drug Act in 1983, the population of the United States has grown considerably (from ~230 million to ~320 million, or ~40%), suggesting that the spirit of the law is to facilitate drug development for conditions with prevalence greater than 200,000 in the United States today. As such, ICER's selection of 10,000 as the threshold patient-population size appears at odds with consensus reached in the literature and prevailing legislation, which indicate that diseases with patient population significantly larger than 10,000 are impacted by challenges in evidence generate and commercial viability.

The selection of a fixed threshold is also of concern because evidence suggests that the impact of small patient populations on commercial viability is continuous in the population size. It appears arbitrary to assume that the challenges of drug development for rare diseases would meaningfully differ for a patient population of 9,000 versus for one of 11,000. Per Acemoglu and Linn (2004)[13], innovation in the pharmaceutical industry, specifically the entry of new molecular entities (NMEs), has been observed to be driven by market size/profit opportunity for the innovation. Importantly, Acemoglu and Linn estimate a *continuous* relationship between market size and innovation (reporting that a 1% increase in market size was associated with a 4%-6% increase in NMEs from 1970-2000). The conclusion that, "only when patient populations near a smaller size of approximately 10,000 individuals does it seem that assessment methods might need to change in some way", seems to infer discontinuity in the impact of market size on innovation, which does not appear to be borne out in the empirical literature.

Thus, while ICER may only see the need to change assessment methods to challenges in evidence generation when patient populations are lower than 10,000, the lack of adjustment of assessment methods for diseases with patient populations between 10,000 to 200,000 yields inconsistency between law governing orphan-drug development (i.e., the Orphan Drug Act) and market-access assessment methods (e.g., ICER's long-term value and value-based price recommendations). As observed by Drummond et al. (2007)[14], "[i]t does not make much sense (in terms of efficiency) for the public system to fund or subsidize R&D on orphan drugs and later not reimburse the resulting innovations. This strategy will lead to a waste of R&D resources (if the products are finally not used) and discourage future investment on R&D on orphan drugs." Consistency should therefore be sought between regulatory-approval and market-access assessment methods.

In addition, the third criterion, requiring "major gain in improved quality of life and/or length of life," may be difficult to implement in an unbiased manner in practice. In clinical trials that investigate therapies with the potential for major gains in quality/length of life, the ethical tension between the quality of control data and the patient's significant unmet need is particularly likely to require reliance on historical-control data rather than placebo controls, a fact that ICER recognizes ("The commonly used approach of evaluating major advances for severe ultra-rare conditions against historical controls will be highlighted."). As a result, comparative effectiveness results are likely to be viewed as more uncertain,

[13] Acemoglu D, Linn J. Market size in innovation: theory and evidence from the pharmaceutical industry. Q J Econ. 2004;119(3):1049-1090.

[14] Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007 Winter;23(1):36-42.

raising the question of whether therapies for URD are likely to yield major gains in quality/length of life in the long-run. By this fundamental challenge in trial design for URD products, accuracy and consistency of application of the third criterion may be rendered challenging for UODs.

Section 1.2 from Proposed ICER Framework

> **ICER will include in its initial draft scoping document a recommendation on whether a treatment meets the above criteria. Following formal public comment, ICER will make a final decision on whether the treatment meets these criteria and will therefore be appraised using an adapted approach.**

Spark Response

We agree with ICER's proposal to provide a transparent process, subject to public comment, regarding the framework that will apply to assessing a treatment. From a process point, however, as noted above, we are concerned that ICER has issued scoping documents, particularly for VN, stating that the adapted approach will be used before the adapted framework is finalized. We urge ICER to follow protocols and timelines in the future that will ensure that framework updates and modifications are complete prior to proposing their use for assessments.

Section 2.1 from Proposed ICER Framework

> **For assessment of the comparative clinical effectiveness of potential major advances for serious ultra-rare conditions, ICER will not change its approach to rating evidence according to the ICER EBM matrix, nor will there be different "standards" of evidence. Instead, ICER will provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit. The commonly used approach of evaluating major advances for severe ultra-rare conditions against historical controls will be highlighted**.

Spark Response

Spark appreciates the plan for ICER to "provide specific context regarding the potential challenges of generating evidence for these treatments, including considerations of challenges to conducting RCTs, to validating surrogate outcome measures, and for obtaining long-term data on safety and on the durability of clinical benefit." These challenges are certainly present for many potential therapies for URDs, and appear to be important elements in the characteristics of evidence that ICER recognizes as impacting certainty of evidence.[15]

However, given that these challenges are generally recognized for therapies for URDs, it is unclear why they would still be factors included in ICER's Evidence Rating Matrix for Comparative Clinical Effectiveness. The portrayal of evidence surrounding UOD products as uncertain often is used by payers in price negotiations with manufacturers; as such, the decision to remark on these common challenges, rather than to adjust the standards of evidence considered in the adapted framework, may disadvantage manufacturers of URD products in negotiations with payers.

[15] Ollendorf DA, Pearson SD. ICER Evidence Rating Matrix: A User's Guide [Internet]. 2017. ICER. Available at: http://icer-review.org/wp-content/uploads/2016/02/Rating-Matrix-User-Guide-UPDATED-06.30.17.pdf

Section 3.1 from Proposed ICER Framework

> **For assessment of cost-effectiveness of a potential major advance for a serious ultra-rare condition, ICER will seek to produce a cost-effectiveness model for every new treatment, acknowledging and highlighting additional uncertainty in translating patient outcomes into quality-adjusted life year (QALY) measures.**

Spark Response

As indicated above, the portrayal of evidence surrounding UOD products as uncertain may potentially disadvantage manufacturers of URD products in negotiations with payers. Nonetheless, Spark appreciates that for payers facing resource constraints, cost-effectiveness analysis may provide useful information.

Given the inherent challenges in performing robust and unbiased cost-effectiveness analysis for URD products, it is our view that it would better serve as an initial tool to allow payers to identify the clinical outcomes that would particularly drive value, such that these outcomes can be monitored and additional data collected in order to help payers make better-informed decisions regarding the long-term value of the product. This could be implemented by using cost-effectiveness analysis to identify parameters/outcomes most significantly driving the potential long-term value of UODs. Such parameters could then be tracked in registry analyses and/or used to structure outcomes-based-payment/pay-for-performance agreements.

Section 3.2 from Proposed ICER Framework

> **For these treatments ICER will adapt its analyses to provide willingness-to-pay threshold results for a broader range, from $50,000 per QALY to $500,000 per QALY. No special quantitative weighting system will be applied to different magnitudes of QALY gains or to baseline severity of the condition.**

Spark Response

Spark appreciates that the range of willingness-to-pay thresholds for which results will be considered is expanded at the high end to $500,000. However, if a reviewer of ICER's reports is not provided guidance regarding the most appropriate willingness-to-pay threshold to consider, we are concerned that inclusion of these additional results below will be of limited impact. For instance, unless provided with additional context supporting the appropriateness of higher willingness-to-pay thresholds for UODs (please see the response to Section 3.3 below), a reader would not have a basis for differentiating between results at a threshold of $50,000 versus at $500,000 per QALY. Further, given ICER's proposal not to adjust value-based price benchmarks (see Section 3.3) and the $175,000 per QALY threshold used for long-term value determinations (see Section 6.1), the implicit signal to reviewers is that the $500,000 per QALY threshold is no more relevant for UODs than it would be for treatments of more common diseases.

Section 3.3 from Proposed ICER Framework

> **ICER will calculate a value-based price benchmark for these treatments using the standard range from $100,000 to $150,000 per QALY, but will add language in all report formats indicating that decision-makers in the US and in international settings often give special weighting to other benefits and to contextual considerations that lead to coverage and funding decisions at higher prices, and thus higher cost-effectiveness ratios, than applied to decisions about other treatments.**

Spark Response

Spark disagrees with the appropriateness of applying the standard range from $100,000 to $150,000 per QALY as the basis for calculating value-based price benchmarks for URD products. The implication of doing

so is that no more should be paid for health benefits experienced by patients with URDs than for those experienced by patients with more common diseases. This implication is at odds with orphan-drug legislation, which seeks to facilitate commercial development of therapies for rare diseases.

Further, limitations to market access of URD products, based on the higher costs they require to be commercially viable, may yield inefficiencies in light of societal investment to research and support these diseases and patient populations. As observed by Drummond et al. (2007)[16], "[i]t does not make much sense (in terms of efficiency) for the public system to fund or subsidize R&D on orphan drugs and later not reimburse the resulting innovations. This strategy will lead to a waste of R&D resources (if the products are finally not used) and discourage future investment on R&D on orphan drugs."

Finally, the use of the same cost-per-QALY range as the basis for calculating value-based price benchmarks implies that willingness to pay is consistent across health benefits of all types, while studies of societal preferences indicate otherwise. Preferences have been shown for giving priority to treatments for more severe and urgent conditions.[17] Some studies have also indicated a preference for assigning a higher priority to treatments for younger patients (although it has been difficult to quantify the magnitude of this preference),[18] and for patients with rare diseases.[19]

To reflect societal preferences in the determination of value-based price benchmarks, QALY calculations should be weighted. As described above, the HTA bodies in England and the Netherlands (NICE and ZiN, respectively) have taken steps to weight QALY gains by adjusting cost-per-QALY threshold for magnitude of incremental QALY gains and for disease severity, respectively.[20] While challenges persist around how to implement QALY weights and how to identify and set the appropriate willingness to pay for URD products, efforts should be made to better account for societal preferences in allocation of healthcare budgets.

Section 3.4 from Proposed ICER Framework

> **When ICER 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**

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[16] Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007 Winter;23(1):36-42.

[17] Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22(8):948-64.
Nord E. Cost-value analysis in health care. New York: Cambridge Press; 1999.
Dolan P, Shaw R, Tsuchiya A, Williams A. QALY maximisation and people's preferences: a methodological review of the literature. Health Econ. 2005;14(2):197-208.
Brazier J, Ratcliffe J, Tsuchiya A, Salomon J. Measuring and valuing health benefits for economic evaluation. Second ed. Oxford: Oxford University Press; 2007. 287-96.

[18] Tsuchiya A. The value of health at different ages. Discussion Paper No. 184. University of York Centre for Health Economics2001.
Tsuchiya A, Dolan P, Shaw R. Measuring people's preferences regarding ageism in health: some methodological issues and some fresh evidence. Soc Sci Med. 2003;57(4):687-96.

[19] Drummond MF, Towse AK. Orphan drugs policies: a suitable case for treatment. Eur J Health Econ. 2014;15:335-40.
Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. Health Econ. 2013;22(8):948-64.

[20] Raftery J. NICE's proposed new QALY modifier for appraising highly specialised technologies The BMJ Opinion2017 [updated 18 April 2017. Available from: http://blogs.bmj.com/bmj/2017/04/18/nices-proposed-new-qaly-modifier-for-appraising-highly-specialised-technologies/.
National Institute for Health and Care Excellence. NICE gets go-ahead to fast-track more drug approvals NICE2017 [updated 15 March 2017. Available from: https://www.nice.org.uk/news/article/nice-gets-go-ahead-to-fast-track-more-drug-approvals.
Zwaap J, Knies S, van der Meijden C, Staal P, van der Heiden L. Cost-effectiveness in practice. Zorginstituut Nederlands; 2015 26 June 2015.

value-based price benchmark. Instead, ICER will provide a crosswalk to a cost-consequence price for a treatment and condition pair that is the closest clinical analogue that can be found.

Spark Response
To facilitate translation of patient outcomes into QALYs, Spark recommends that ICER conduct systematic literature review to identify "mapping" studies which may facilitate translation of disease-outcomes measures to QALYs. In the future, ICER may benefit from conducting such mapping studies for outcomes measures for which translation to QALYs (e.g., mapping to EQ-5D) are not available or uncertain.

Section 4.1 from Proposed ICER Framework

For report sections on "other benefits and disadvantages" and "contextual considerations," ICER will include a broader frame to seek evidence and perspective on the potential for these treatments to affect positively the family, school, and community. Information will also be sought on the potential impact of new treatments on the infrastructure for screening and care of the affected individuals.

Spark Response
ICER should include family-borne costs (e.g., caregiver burden in costs and health utility) in its base case analysis, unless it can confirm that private payers in the United States do not consider such aspects of insurance benefits when designing and offering insurance coverage. There is great evidence to the contrary, including the offering of spousal or family coverage to a prospective insured. Further, if private payers are interested in the extra-familial, societal effects of their coverage decisions, such as the effects of educational attainment for a child with a UOD in the presence and absence of treatment, societal aspects of the model should be included in the base case.

Spark supports the inclusion of "other benefits and standards" and "contextual considerations" for inclusion in the framework. Spark strongly agrees with the need for consideration of factors outside of the disease state that are additive to the overall value of a treatment. Both indirect and direct costs of diseases and disorders impede patients, their families and caregivers, health systems, education systems, and governments attempting to mitigate the infliction.

For example, eye disorders have an impact on a wide spectrum of medical and non–medical benefits and costs. Spark has reviewed the landmark study conducted by the National Opinion Research Center (NORC), an independent research institution at the University of Chicago that estimates the economic burden of eye problems in the U.S. NORC found that the annual total economic burden of eye disorders and vision loss is $139 billion, based on the 2011 U.S. population in 2013 dollars. These total costs breakdown into $66.8 billion in direct costs (48% of total costs) and $77.2 billion of indirect costs (52% of total costs).[21]

Direct costs are incurred by the patient, providers, education system, health systems, insurers, as and state and federal governments. Direct costs for vision disorders may include: medical costs for diagnosed disorders; medical costs attributable to low vision; medical vision aids; assistive devices and adaptations, and direct services such as special education and assistance programs. Diagnosed medical cost is the largest direct cost, followed by medical vision aids, undiagnosed vision loss, assistance devices, education/school screening, and assistance programs. As highlighted by the ICER Orphan Drug Assessment and Pricing Summit, schools play a critically important role in supporting rare-disease patients

with individualized education plans and in-classroom assistance from not only teachers, but caregivers and aides. Schools also may provide specialized equipment to assist student learning and facilitate a learning environment that best suits students' needs.

Indirect costs may be as debilitating as the direct costs associated with vision loss, particularly for the patient and his or her quality of life. Consequences of low vision may include, as productivity losses, long-term care, informal care, and costs of transfer and entitlement programs. The vast majority of indirect costs are attributable to productivity loss and nursing home care.

Section 5.1 from Proposed ICER Framework

> **ICER will conduct over the coming year a collaborative process through which it will seek to develop a template for providing information in its reports on the research, development, and other relevant costs related to new treatments for serious ultra-rare conditions. Until this template is completed, ICER will work with individual manufacturers of treatments under review to determine what, if any, information related to the costs of development can be shared as part of the public deliberation regarding the value of these treatments and their appropriate pricing.**

Spark Response

Spark objects to ICER's proposal to attempt to collect this information from manufacturers. As a private third-party entity, ICER does not have the authority to seek or publish this type of competitively sensitive information. The organization also lacks sufficient safeguards to ensure any information given to ICER would remain confidential.

Further, the position that "appropriate pricing" may be inferred based on collection of research, development, and other costs related to new treatments for serious ultra-rare conditions misrepresents the business model of continued innovation (i.e., not a cost-recovery model). Many manufacturers develop multiple product lines simultaneously, with a discovery in one area informing investment in another. In the pre-clinical phase, a company may make broad-based investments that have significant impact over time but are not linked to any one product in particular. Prices for approved medicines must also account for the research and development of those products that are investigated but ultimately fail. Finally, mergers and acquisitions, licensing, and joint development arrangements would greatly impede the development of any common template that could be used across different products. Isolating the research and development costs for any one product would therefore be extremely difficult – if not impossible – and not constitute a sound basis on which to judge "appropriate pricing".

Section 6.1 from Proposed ICER Framework

> **During public meetings of ICER's independent appraisal committees, votes on the "long-term value for money" of treatments for serious ultra-rare conditions will be done according to the same procedures for other interventions, i.e. if the base case estimate falls between $50,000-$175,000 per QALY. However, for treatments of ultra-rare conditions, ICER will not assign any designation of value if the base case cost-effectiveness ratio is above $175,000 per QALY.**

Spark Response

Spark appreciates that, by contrast to ICER's general framework, URD drugs with cost-effectiveness ratios above $175,000 per QALY will not explicitly be "deemed 'low value' without formal voting by the committee." Nonetheless, given the public availability of ICER's framework for ultra-rare conditions, it seems that an informed reviewer of ICER reports on URD products may reasonably infer that when ICER does not assign any designation of value, the implication is that in the long term the product is not of 'high

value'. Alternatively stated, the use of the same cost-effectiveness thresholds as in ICER's general assessment framework for assigning designations of long-term value may imply that products with cost-effectiveness ratios above $175,000 are not 'high value', even if ICER does not explicitly state so.

Conclusion

Spark appreciates the opportunity to comment on the "Proposed Adaptation of the ICER Value Framework for the Assessment of Treatments for Ultra-rare Conditions." We urge ICER to consider our concerns and recommendations, particularly when reviewing the proposed criteria for consideration and weighing how they will be implemented. We support incorporating "other benefits and standards" and "contextual considerations" for inclusion in the revised framework, and recommend that ICER conduct systematic literature reviews to identify "mapping" studies which may facilitate translation of disease-outcome measures to QALYs. Furthermore, we encourage ICER to exercise caution when assigning value thresholds for URDs under this framework. We would be pleased to answer any questions ICER may have regarding these comments.

Please do not hesitate to contact me [contact information redacted for posting] with any questions.

Sincerely,

[*Electronic Signature*]

Sarah Pitluck
Head, Global Pricing & Reimbursement