Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value

Response to Public Comments on Draft Evidence Report

March 15, 2018

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#	Comment	Response/Integration
Manufacturers		
Genentech		
1.	Model validity will be enhanced by greater use of HAVEN 1 data to better represent efficacy outcomes of treatment with BPAs compared to emicizumab in patients with hemophilia A with FVIII inhibitors, as well as the use of consistent cost sources. The efficacy of emicizumab compared to prophylaxis with bypassing agents (BPAs) should be based on the intra-patient comparison for patients from the non-interventional study (NIS; NCT02476942) who switched to emicizumab (Arm C - HAVEN 1) The intra-patient comparison (comparing NIS data to Arm C of HAVEN 1) is the only data source that compares the efficacy of BPAs to emicizumab. As communicated in prior responses, we believe that the NIS is the most current and relevant source of data to inform model assumptions around the utilization and outcomes in patients with hemophilia A with FVIII inhibitors for the following reasons: ● The NIS is the largest and most recent clinical study of patients with hemophilia A with FVIII inhibitors to date. ● The intra-patient comparison captures the treatment comparisons of emicizumab versus the class of BPAs that ICER seeks to evaluate. ● The NIS has greater generalizability to a real-world population. The current model is limited by the assumption that all BPAs are equivalent based on the PROOF trial. However, only activated prothrombin complex concentrate (aPCC) was evaluated in the PROOF trial. The assumption that all BPAs are equivalent when used for prophylaxis in patients with hemophilia A with FVIII inhibitors is not supported by head-to-head clinical trials. We strongly encourage ICER to consider the above points around efficacy assumptions in order to more comprehensively represent the treatment interventions of interest.	We disagree that intra-patient comparison from HAVEN 1 is the most appropriate measure of the relative effectiveness of emicizumab compared with BPAs. These observational data are informative but are at high risk for bias because they reflect a treatment prior to an interventional study compared with an intervention during a study. Although direct comparisons across the interventional trials are also problematic, we feel that comparing results seen in RCTs is the most appropriate way to compare emicizumab with BPAs. We agree that the assumption that all BPAs are equivalent is not supported by an RCT looking at prophylaxis with BPAs, and this limitation is noted in the report.
2.	Consistent sources for drug price must be used to ensure fair and balanced comparisons. The current model uses different pricing sources by comparing the wholesale acquisition cost (WAC) of emicizumab with the average sales price (ASP) of recombinant activated factor VII (rFVIIa) and aPCC. ASP is a discount of WAC, and combining these different prices biases the comparison of one intervention over the other. Currently, WAC is the only available price for emicizumab. We recommend that ICER conservatively assume WAC for all treatments in order to maintain consistency in its comparisons.	Using WAC for interventions that have known ASP would not reflect realistic costs for these interventions. WAC is the only available price for emicizumab, as its potential discounted price is unknown. We therefore chose to use WAC for emicizumab as a conservative assumption and estimated that emicizumab would be cost-saving even using this conservative assumption around pricing. If provided with any data on a potential discount for emicizumab, we can consider modeling emicizumab at a discounted price.

3.	ICER should ensure consistency by using efficacy measures based on the same statistical approach. As acknowledged in the draft report, the statistical approach to calculate bleed outcomes varies significantly in hemophilia trials. ICER's model uses two different values to characterize the efficacy of treatment comparators by comparing the median treated annualized bleed rate (ABR) for patients receiving aPCC prophylaxis with the adjusted mean ABR for emicizumab. The median and mean ABR calculations estimate different rates of bleed events and should not be compared unless it's known the cohort distributions are symmetrical. Adjusted mean and median ABRs for emicizumab are presented in table 1. (See Table 1)	We believe that using mean ABRs is preferable, however these are not available in the PROOF trial. There are a number of limitations in the data from PROOF and we recognize that we are applying a RR based on the difference in median ABRs as an estimate of a RR derived from mean ABRs.
4.	Adverse events associated with the treatments of interest should be accurately represented in the evidence report in order to prevent misinterpretation of safety profiles. 'Thrombotic microangiopathy' should be used throughout the report to accurately reflect the adverse events reported in HAVEN 1. Increased specificity of adverse event reporting will result in a more accurate representation of emicizumab's safety profile. The Draft Evidence Report often refers to 'thrombotic and microangiopathic events'. This inaccurately represents the serious adverse events observed in HAVEN 1 because microangiopathy is a broad term that refers to any small vessel disease. In HAVEN 1, only thrombotic microangiopathy, which results in thrombosis in capillaries and arterioles, was reported. We suggest aligning with the terminology used in the ICER report to that used in the HAVEN 1 publication (thrombotic microangiopathy or thrombosis) or the Hemlibra prescribing information (thrombotic microangiopathy and thrombotic events).	We have made this change in the report.
5.	Patient-centric outcomes and considerations should be expanded to better capture the impact of emicizumab to patients, caregivers and communities. Genentech acknowledges the importance of capturing outcomes that are important to patients. We are committed to investing in patient-centric research to fully characterize the benefit of emicizumab in the real-world setting. We suggest expanding section 5.1 in the Draft Evidence Report by including additional patient-centric considerations available in published literature.	We have included newer data on patient-centric outcomes in section 3 of the report.
6.	Burden of treatment administration and impact to adherence is an important consideration for patients and caregivers. Genentech appreciates ICER's discussion of the burden of treatment administration, particularly given the life-long duration of hemophilia. In Section 5.1 of the report, we suggest that ICER include a statement acknowledging that intravenous administration has been identified in the published literature as a key barrier to starting and adhering to prophylactic therapies in patients with hemophilia.	We have added this to section 5.1

7.	Consider including recently-presented, patient-centric data from the HAVEN 1 and HAVEN 2 clinical trials. In response to the report's statement that no published data are available on the impact of emicizumab prophylaxis on missed work or school days and hospitalization, we provide exploratory data that was recently presented at the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders (EAHAD) in Tables 2, 3 and 4. (See Tables 2,3 and 4) Adults and adolescents treated with emicizumab prophylaxis had numerically fewer missed work and school days when compared to those on episodic BPAs in HAVEN 1. Additionally, school and daycare attendance numerically improved after children began receiving emicizumab. Patients treated with emicizumab prophylaxis had numerically fewer hospitalization days when compared to adults and adolescents on episodic and prophylaxis BPAs in HAVEN 1. The number of days hospitalized from start of HAVEN 1 through Week 25 are presented in Table 4.	We have now included data from recent presentations on patient-centric outcomes in trials of emicizumab.
8.	Use emicizumab-kxwh at first mention, use FDA-approved generic name	We have made this change in the report.
9.	Change table 3.1 - "HAVEN 1 period 24 weeks" to at least 24 weeks	Thank you for the correction. We have now made this change in the report.
10.	Change table 3.2 - "p value for treated joint bleeds is reported as <0.0001" to p=0.0050	Thank you for the correction. We have now made this change in the report.
11.	Page 39- "Patients had to have at least 6 bleeding events on BPA prophylaxis prior to study entry" change to - Patients had to have at least 2 bleeding events on BPA prophylaxis prior to study entry	We have removed this sentence from the section on Controversies and Uncertainties. The description of the entry criteria was accurate in the main description of HAVEN 1.
Shire		
12.	The title of the report "Emicizumab for Hemophilia A: Effectiveness and Value" is inaccurate, as the evaluation is specific to Hemophilia A patients with inhibitors. The value and affordability of emicizumab in non-inhibitor patients has not yet been evaluated.	Thank you for this suggestion. We agree and have updated the report title to be 'Emicizumab for Hemophilia A with Inhibitors'

13.	Many new products brought to market to address patients' needs in a disease area can be proven safe and effective for FDA approval, but still be in the process of developing more data needed for value assessment. This is particularly true in the case of rare diseases such as hemophilia A with inhibitors. In cases where products show great promise for treating rare disease in which they may have limited data, ICER should cautiously review these technologies until adequate information is available and outcomes in real-world practice become more widely available. It is not appropriate to pass judgement on a new technology with limited data. Patient safety remains Shire's first priority. In addition to clinical studies, we support the use of real world evidence in the ICER value assessment. FEIBA has a well-established safety profile developed over 40 years and spontaneous reporting rate of thromboembolic events (TEEs) of less than 0.005%. In 103 patients in the emicizumab Phase III trial, 2 (1.9%) TEEs and 3 thrombotic microangiopathy (2.9%) were observed with 1 of the TMA event leading to a fatal rectal hemorrhage. Due to the limited clinical data and lack of real world experience, the rate of these serious adverse events with emicizumab in a larger, heterogeneous population for longer durations is unknown. To our knowledge, there has been no TMAs related to FEIBA use alone.	We review emerging therapies at or near the time of FDA approval in order to inform decision makers who need to make judgments based on the best available evidence. We agree that there remain important safety questions with new therapies such as emicizumab. We note this issue in several places in the report. However, we believe that it is important to have a transparent and public conversation with all stakeholders about the existing data, including potential uncertainties and gaps in the data, in order to aid decision makers who need to make judgments at the time of approval.
14.	We reassert that lack of sufficient evidence precludes conclusive comparative effectiveness analysis and economic modeling. Unlike more common diseases, value assessment in rare diseases, such as hemophilia A with inhibitors, is challenging due to the small and heterogeneous patient population, leading to a dearth of scientifically robust data. The small population also results in a lack of randomized study designs across products, requiring indirect comparison among small individual product studies where endpoints and populations can be different. These limitations for rare diseases can lead to greater uncertainty when applying the cost per QALY threshold for treatments. There are 4 published randomized controlled clinical trials for the prophylaxis treatment of hemophilia A with inhibitors. These trials have substantial differences in trial design, patient population, comparators, endpoints and supportive care, making it extremely challenging to conduct conclusive clinical effectiveness analysis, and subsequently meaningful cost-effectiveness analysis. Hemophilia A with inhibitors is an orphan condition in which treatment decisions require complex and personalized clinical, safety, and ethical considerations. It would be inappropriate to consider the current base case model results as a part of therapy decision-making without understanding how variable the results can be based on clinical assumptions made.	We agree that there are limitations in the available evidence. In the evidence review, we evaluate the quality of all evidence, and consider the differences in trial design, study populations, outcomes, endpoints, and supportive care in order to make our ultimate determinations regarding the evidence ratings. In the model, we chose the most favorable results of a randomized trial of BPA prophylaxis to include in our analyses and modeling. This represents a conservative approach since we chose the most favorable estimates for BPAs in our model.

15.	To reflect normal clinical practice, we reassert that this evaluation should compare emicizumab to aPCC and rFVIIa as separate bypassing agent (BPA) comparator arms rather than combining them together as a BPA arm. The BPA arm of the model should be separated into distinct aPCC and rFVIIa treatment arms. While aPCC and rFVIIa are both categorized as BPAs, there are substantial and well-recognized differences in mechanism of action, prophylaxis efficacy, dosing, and unit cost between the two. Importantly, while aPCC is indicated for prophylaxis, rFVIIa is not. Comparing emicizumab to a generic BPA prophylaxis grouping does not provide an adequate level of evidence necessary for practical use of the analysis results, as evaluation of treatments are made based on individual product benefits and risks. For a payer, given that the cost of aPCC prophylaxis is half that of rFVIIa prophylaxis based on dosing used in the model, a combined BPA grouping inappropriately links aPCC with a high cost. Particularly for complex conditions such as hemophilia A with inhibitors, assessment of treatments should be left to clinical experts, who can be expected to provide guidance on the continual evolution of the standard of care and the nuance of individual clinical decision making. The complexity of tailoring different treatment options for different population under various treatment settings should be directed by the clinical community through guidelines and peer-reviewed publications.	In the base case analysis, we used a weighted average approach to account for the observed proportions of patients receiving either aPCC (33%), or rFVIIa (52%) or both (15%), based on arms A and B from HAVEN 1 (see Table 4.5). We consider this weighted approach most appropriate to derive the overall estimate for a BPA prophylaxis strategy. In addition, we modelled a scenario (the BPA-favoring scenario), in which aPCC prophylaxis is the only BPA considered in the BPA prophylaxis strategy, and we have made a number of additional changes to the emicizumab and BPA strategies that favor a 100% aPCC prophylaxis (and on-demand) strategy compared to emicizumab. While the degree to which emicizumab is cost-saving differs in these scenarios, the conclusion remains essentially the same. We also note that while the specific results of this scenario analysis are presented toward the end of the document, we do include a prominent write-up of our approach in the Methods section. Please also see the below response to the next question.
16.	Elements of the “BPA-favoring scenario” are more reflective of real-world hemophilia care and outcomes and should be included in the base case model. ICER has considered the cost of aPCC prophylaxis only in a separate “BPA-favoring scenario” which results in an overall 53% lower estimate of BPA costs. In addition to eliminating the use/cost of rFVIIa, this scenario considers: 1. All bleeds on emicizumab are treated with rFVIIa and all bleeds on aPCC prophylaxis are treated with aPCC. 2. Emicizumab adherence is 100% and aPCC adherence is 88% (applied to cost only) 3. The disutility applied to bleed events is limited to 2 days and the “No Bleed” utility is applied for the remaining 5 days of each model cycle. 4. The rate of thrombotic and microangiopathic events is as reported in HAVEN-1. We strongly believe that compared to the base case model, the “BPA-favoring scenario” is a closer representation of how hemophilia is managed with aPCC and generally how hemophilia impacts patients. We ask that these assumptions be incorporated into the base case model, rather than its current position as a scenario included on page 122 of a 124-page document.	We disagree. We made our decisions on the base case making choices that we felt were most appropriate based on clinical expertise. The base case did not make choices that favored any one therapy. For instance, we heard from some experts that the disutility of a bleed should be longer than one week and that the rate of adverse events with emicizumab should be expected to be lower than seen in HAVEN 1 given changes in protocols and the preliminary experiences in HAVEN 2. Additionally, as discussed above, we used rates of reductions in bleeding based on the PROOF trial rather than intra-patient comparisons from HAVEN 1. All these are favorable to BPAs and are in the base case. The BPA-favoring scenario was created to address specific questions raised, but it is a scenario that we think is much less likely than the base case model.

17.	The wording for voting questions 4d and 4e should reflect a comparison to "currently used bypassing agents" instead of "supportive care". Since bypassing agents, rather than supportive care, are considered the standard of care for Hemophilia A patients with inhibitors, the comparison of long-term risk and magnitude or durability of long-term benefits should be relative to bypassing agents, not supportive care.	Thank you, we have changed the wording of those two voting questions.
18.	Product discounts presented in the model do not accurately reflect manufacturer discounts. Table 4.6 (p.44) incorrectly minimizes actual product discounts, as the actual ASPs are lower than what was represented.	We derived net prices from average sales prices (ASP) using 2017 data for the BPAs to calculate treatment-related health care costs, since we did not have data on net prices that included discounts/rebates for these agents. The link to the cite is https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-Drugs/McrPartBDrugAvgSalesPrice/2018ASPFiles.html
Grifols		
19.	at top of page 14 – the report acknowledges the difficulty with high-titer inhibitors, but only refers to use of by-passing agents (BPAs). In the report's reference #50, National Hemophilia Foundation's (NHF) Medical and Scientific Advisory Council (MASAC) makes the statement: "For high-titer inhibitors, immune tolerance induction is the best option for inhibitor eradication." While the report does not address immune tolerance induction (ITI), we think that ICER should acknowledge that NHF's MASAC has stated that ITI is the best option to eradicate FVIII inhibitors	We acknowledge that ITI is the only option for inhibitor eradication. However, the issue of whether attempting to eradicate inhibitors is appropriate in all patients with high titer inhibitors was an issue of disagreement among experts we consulted.
20.	3.1 Overview, Harms, at top of page 17 – the report lists "Thrombolytic events." We think that you mean "Thrombotic events."	Thank you for this correction.
21.	3.3 Results, 4th paragraph down, page 32 – We are not sure why there is a statement (concerning ITI) made that is unrelated to the model used in the evaluation. It is pure speculation that emicizumab may be used to defer or replace ITI. Because the efficacy and safety of such an approach is unknown at this time, we recommend deleting this paragraph	Thank you. This is in the section on Controversies and Uncertainties and reflects expert input we received about possible future uses of emicizumab. We are choosing to highlight this as a limitation in the report.
22.	4.2 Methods, Key Model Characteristics and Assumptions, entire section – we applaud ICER for the use of both a lifetime time horizon and costs and outcomes over a 5-year time horizon. Lifetime costs are not always considered when making treatment decisions that can have such a life-long and significant impact.	Thank You. The ICER reference case states including a lifetime time horizon in the cost-effectiveness model. Similarly, our reference case states calculating the budget impact of a new intervention over a five-year time horizon.

23.	5.1 Other Benefits, page 64 – each of these areas of potential benefit are reasonable given the concept of a once-a-week subcutaneous administration. However, one area that is not addressed in the draft report is that of bleeding and discerning between a true bleed and an injury that causes pain without significant bleeding. According to MASAC guidance, patients have been instructed on home administration of BPAs whenever they experience a bleed. However, MASAC has issued interim guidance on the use of emicizumab that describes the need for reassessment of bleeds and pain in patients who are receiving emicizumab, since the bleeding phenotype will likely be changing to a milder one. Additionally, 30+ percent of patients in the HAVEN-1 study had bleeds while taking emicizumab. Because of this, and the fact that there is little long-term data or experience with emicizumab, it seems purely speculative at this time that the changes in the quality of life that have been concluded by ICER will be so transformative.	In speaking with patients, providers, and caregivers, we heard that the reductions in treated bleeding events seen with emicizumab (and in the percentage of patients who had any treated bleeding events) were likely large enough to affect decisions about work, school, and recreation for many patients.
24.	5.2 Contextual Considerations, last bullet on page 64 – While this statement is true, it appears "out of context" with the report. None of the products currently in the market today were in the market at the time of this tragedy in the blood supply and in the hemophilia community specifically. There have been significant improvements in therapeutics since that time, including improved screening of plasma donors, enhanced manufacturing processes and the development of recombinant factor products. The report is a comparative effectiveness report of current treatments for patients with inhibitors, not a comparative effectiveness report with treatments for hemophilia from the 1970s and 1980s. We recommend deleting this bullet.	We feel that prior iatrogenic harms in the community of patients with hemophilia create context that stakeholders (including private and public payers) might want to take into account when assessing the value of a treatment for hemophilia. Nothing in this assessment is meant to cast aspersions on earlier therapies for hemophilia that turned out to carry important risks.
25.	7.3 Results, bottom of page 69 – It is clear that the report is "…applicable to a specific population (i.e., those with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful) …" but the report ignores another segment of the population – those who will be treated with ITI. We suggest revising this sentence to read: "As stated in earlier sections of this report, the results of this analysis are applicable to a specific population (i.e., those with hemophilia A with inhibitors to factor VIII who will not be treated with ITI or for whom ITI has been unsuccessful), and not to those who may be treated with ITI or to the broader population of patients with hemophilia A who do not have inhibitors."	Thank you. This sentence has been changed to clarify that results are not applicable to patients who would be treated with ITI.

Patient Groups		
National Hemophilia Foundation and Hemophilia Federation of America		
26.	On page 13 of the draft report, ICER states: "Since BPAs are covered as a medical benefit, patient groups expressed concern about patient out-of-pocket costs in the form of co-insurance and deductibles, although patients with inhibitors already regularly reach their annual out-of-pocket maximums." HFA would like to clarify this statement. Data from Project CALLS shows that many BPAs are covered under the medical benefit AND that patients are worried about increased out-of-pocket costs. Patients with hemophilia, particularly inhibitor patients, are consistently worried about the cost of treatment, wherever the benefit is covered. CALLS data shows an even split between BPAs being covered under the pharmacy benefit, the medical benefit, and patients not knowing which benefit (although our understanding is that BPAs are most commonly covered under the medical benefit)	Thank you. We have clarified this nuance in the report.
27.	In the draft report, ICER indicates that it was unable to find clinical studies in published or unpublished form that discuss the impact of Emicizumab on various aspects of patient and caregiver quality of life. We wish to highlight two additional publications that have been released since ICER began its review, which provide additional data not previously available: • The Emicizumab Prophylaxis and Health-Related Outcomes in Persons with Haemophilia A (PwHA) with Inhibitors: HAVEN 1 Study poster presentation from the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders found that study participants on Emicizumab on prophylaxis had higher quality of life scores – as measured by the Haemophilia-specific quality of life (QoL) instrument in adults (Haem-A-QoL) – than did individuals not on prophylaxis, specifically in the "school and work" and "family" domains. These individuals also reported fewer missed days of school and work. The poster cites "substantial and meaningful differences in the daily lives" of people with hemophilia and inhibitors. • The Emicizumab Prophylaxis in Paediatric Persons with Haemophilia A (PwHA) with Inhibitors: Impact on Health-Related Outcomes and Caregiver Burden in the HAVEN 2 Study oral presentation at the 11th Annual Congress of the European Association of Haemophilia and Allied Disorders also provides additional data regarding the impact of Emicizumab on children and caregivers. This study found that children reported improvements in their physical health and feelings using the Haemophilia-Specific Quality of Life Assessment for Children Short Form. Caregivers reported marked improvements regarding several aspects of the caregiver burden, especially with their perception of the child's hemophilia and the impact of the condition on the family life. They also reported significant, sustained improvements in school/daycare attendance	Thank you for bringing the additional publications to our attention. We have now included data on the impact of emicizumab on different aspects of patients and caregivers' quality of life.

28.	4.3 Summary and Comment – Limitations: It is challenging to anticipate the real-world adherence to Emicizumab outside of the structure of the clinical trial setting. Accordingly, it will be important to monitor adherence over time.	We agree and are also interested to see how this unfolds. Given (a) the disease severity in inhibitor patients, (b) the once weekly regimen, and (c) subcutaneous delivery, there's good reason to be optimistic that adherence will be high in this population.
29.	Finally, we wish to emphasize the points made in prior comment letters that the "other benefits and contextual considerations" should remain a primary consideration in ICER's value calculations. While the ultra-rare size of the patient population, combined with the longer time period necessary to fully assess the effects of prophylaxis with Emicizumab on education, employment and careers, we believe that Emicizumab brings a number of other long-term benefits to affected individuals and their families. Personal communications from patients and families who have participated in the Emicizumab trials, along with the data reported in the HAVEN 1 and 2 studies referenced above, suggest that Emicizumab transforms the way people with hemophilia and an inhibitor may now live their lives. Data suggest that Emicizumab has the potential to reduce caregiver and family burden and that it will have a significant impact on improving patients' ability to attend school and work. The subcutaneous administration is also meaningful in terms of reducing complexity associated with treatment, treatment burden and improving patient outcomes. Moreover, it is clear that the intervention is intended for the care of individuals with a condition of high-severity in terms of impact on quality of life, morbidity and mortality. We reiterate our request that ICER prominently discuss these other benefits and contextual considerations in the final report. If not suitable for inclusion within the economic model, we encourage ICER to prominently discuss the added patient-relevant outcomes in any executive summary it produces, rather than leave them to recommendations for future research.	Thank you. These are presented prominently in the executive summary and will be a featured discussion during the public meeting on March 29.

Patients Rising NOW		
30.	We are very aware that the Potential Budget Impact section of ICER's reports has long received considerable attention, but in our view, ICER's process and presentation have not undergone significant nor positive revisions. For example, the concept that it is possible or reasonable to evaluate "the budget" for health care spending in the United States is dubious. That is, while others (CMS, Altarum) routinely evaluate spending on health care in the United States, and they and others (such as CBO or the Federal Reserve) model future or expenditures, the inherent reality of the multi-payer structure of financing of health care in the United States means that there is no specific budget. Of course, there are specific programs and payers that do have budgets for various sectors or populations in the United States: The National Institutes of Health (NIH) has a budget; The Center for Disease Control and Prevention (CDC) has a budget; and the Veterans Health Administration (VHA) has a budget. Other programs have projected expenditures and either draw on trust funds for those payments (such as Medicare Part A), or manage themselves based upon those projections of spending and revenues, such as individual hospitals, health systems, and insurers. It is critical to realize that patient's perspectives involve their costs and their access to care. Thus, regarding budgets and spending, their concerns about the implications of any innovation, or legal or regulatory change, are how such innovations or changes would affect their insurance program, benefits plan, affordability, or access to care.	ICER's budget impact analyses are not meant to imply that there is a unitary budget for health care in the United States. Rather, they are intended to determine whether there is potential for a new intervention(s) to increase health care spending to the point that affordability and access to care may be compromised.

31.	Specific to the Potential Budget Impact section in ICER's draft evidence report concerning hemophilia, there are many, many deficiencies because it treats all health care spending in the United States as one uniform bucket. However, for many diseases, and particularly for hemophilia, this is not true. For example, as an inherited disorder predisposing people to bleeding (and significant complications such as joint damage), it is extremely unlikely that people with hemophilia would pass the physical tests necessary to join the armed services. Thus, the prevalence of people with hemophilia who are patients in the VHA is likely to be very, very small, and certainly much lower than in the general population. Therefore, for the VHA to apply ICER's Potential Budget Impact estimate to their system for veterans would be irrational. Similarly, the prevalence of people with hemophilia who are Medicare beneficiaries is less than the national average. This was shown by the GAO in an older report that found about 6% of Medicare beneficiaries have hemophilia, which is less than half the rate of enrollment in Medicare for the entire population. Similar data shows that by age, hemophilia prevalence skews considerably towards younger segments of the population. (See chart) This skewing of the age distribution makes sense because hemophilia is a genetic condition, and thus, it would also be expected that Medicaid programs would have a higher prevalence of people with the condition. This is reflected in a study of Medicaid and hemophilia that found "30–40% of male patients with hemophilia were covered by Medicare or Medicaid"" indicating that about 24-34% are covered by Medicaid, a percentage that is at least twice that of the non-elderly population enrolled in Medicaid. What this means in term of financial consequences for patients concerned about rising costs and access to care is that any changes in treatment options or payment paradigms, need to be viewed in the context of their individual insurance coverage and clinical situation. Similarly, managers, administrators, and leaders of health care payers and care delivery organizations need to have parallel perspectives. Therefore, in the case of new treatments for hemophilia (such as emicizumab), the financial implications for Medicaid programs (before considering any rebates or discounts) should be greater than any average "budget impact," while the financial implications for Medicare would be less than the average, and the implications for the VHA are essentially negligible. The bottom line is that **presenting a "budget impact" analysis for the health care spending across the entire United States is essentially a fictional story.** Rather, appropriate assessments of financial implications need to be done from the perspective of the individual health plan or insurance company. An extreme (and currently hypothetical) example would be for a health insurance plan that only covered women, e.g., "WomenHI Plan of the US." Since hemophilia is an X-linked genetic disorder, it is rare for a female to have hemophilia. Thus the "budget impact" of new treatments for hemophilia for the "WomenHI	ICER's analyses of potential budget impact are intended to provide an alert if the anticipated cost to the overall health care system has the potential to exceed specific growth targets due to high incremental costs and/or population size. They are not intended as assessments of actual budget impact for any individual payer or program, as each will have different cost structures and enrolled populations. It is understood that individual payers and programs will conduct budget impact analyses specific to their populations and costs.

	Plan of the US" would be very negligible, while the "budget impact" for their brothers' male only plan could be very significant.	

32.	Analyzing Budget Impact v. Modeling Financial or Spending Estimates: As discussed above, there is a significant difference between budgeting (which is done by all sorts of organizations – from families to corporations – to help them plan their activities based upon expected revenues and expenses), and macro-economic modeling that encompasses multiple organizations or entities, such as annual spending on hospital in-patient services. Another very problematic aspect of the methodology ICER uses in its "Budget Impact" section is to assume that a fixed percentage of spending on biopharmaceutical therapies is appropriate. This presumption fails to recognize the perspectives of many, many patients who are suffering with chronic illnesses that severely impair or shorten their lives, and for whom there are no or inadequate treatments. For them, a new treatment may represent not just a dramatic improvement in function, quality of life, or longevity, but also hope – hope that even if the new treatment has modest benefits it will bridge them until the next clinical breakthrough becomes available. The history of HIV infection and AIDS therapies is very illustrative of this concept: In the early 1990s there were only a few antivirals that helped slow the progression of AIDS, and while certainly not adequate, they did provide time for people infected with HIV. That time enabled many to live until the protease inhibitors became available in the mid-1990s, which then provided the basis for combination therapies that offered the first opportunity for controlling HIV infection and significantly longer life. Of course, since then, there have been even more advances making treatment of HIV infection much easier, and with fewer and milder complications. (There are similar examples of this concept in oncology and serious chronic conditions.) We recognize that in the draft evidence report, the budget impact section attempts to model costs foregone when using a new treatment, however, the update to ICER's framework states concerning increased spending for a new treatment includes: "A good discussion might indeed lead to decisions to take further resources from hospitals, nursing homes, physicians, or other dimensions of health care." This statement implies that decisions about resource allocations (i.e., drugs v. hospitalizations) are "made" on a national or even health system-wide basis, but the reality is extremely different. Rather, such substitutions (to use an economists' term) reflect clinical and other benefits rather than management decisions. For example, again using the example of HIV and AIDS, with the advent of the reverse transcriptase inhibitors in the 1990s, the rate of hospital admissions for complications of HIV (such as opportunistic infections) dropped very dramatically. This had significant financial implications (i.e., "budget impact") for hospitals – particularly academic institutions with specialized infectious disease units – causing many of them to reassess their operations and cut back their spending because their revenues from patient care declined significantly. This was not a "a	ICER's budget impact analyses do not "assume that a fixed percentage of spending on biopharmaceutical therapies is appropriate." Rather, they are intended to provide an alert to health care payers and others when an intervention has the potential to cause a rapid increase in spending, so that they can proactively plan for and manage such increases in spending to ensure that access and affordability to new interventions are sustainable over time.

	decision to take resources from hospitals," it was a reality of how an innovation improved patient care, reduced morbidity, and extended the lives of many patients with HIV and AIDS, and dramatically reduced the need for inpatient care.	
33.	An additional point we would like to note is that using FDA's approval numbers for NMEs and BLAs as some sort of appropriate benchmark is curious at best since the actual number can vary significantly from year to year. For example, ICER shows an average of 33.5 approvals in the years 2015-16. However, in 2017 there were 46 approvals, so the 3-year average would be 37.7, and including 2014 data raises the 4-year average to 38.5. We recognize that these higher numbers would reduce the "Annual threshold for average cost growth per individual new molecular entity," but that is the point – from patients' perspectives, more new treatments are a good thing, so building into ICER's Potential Budget Impact model a penalty for more new treatments is completely opposite to patients interests and the movement towards "patient-centered" perspectives in the U.S. health care system, and thus ICER's modeling methodology, is directly anti-patient-centric. For example, if hypothetically 71 new treatments were approved by the FDA in 2019, and 70 of them were for diabetes and one was for Alzheimer's, according to ICER's modelling process, the acceptable budget impact for each of them would be the same – even though it is very questionable that they truly would all result in the same level of spending, particularly since many of the 70 new diabetes treatments would be expected to compete with each other and ICER's model explicitly does not "attempt to estimate the uptake of a new intervention." If such a budget impact analyses were blindly used by payer or health system administrators, they would likely severely restrict access to the one new treatment for Alzheimer's – clearly not in the best interests of patients or society.	ICER clearly does not intend for our budget impact analyses (or indeed any of our analyses) to be "blindly used by payer or health system administrators," regardless of the numbers or types of new medications entering the market. However, on average, a larger number of new interventions entering the market implies that the proportion of growth in costs available for each intervention will be less, unless provision is made for greater growth in costs. Accounting for this is not "a penalty for more new treatments" but rather a recognition that there is likely to be more strain on cost growth when there are many new interventions entering the market than when there are few, and that payers should plan accordingly.

34.	The reality of differential financial implications of new therapies – specifically regarding potential budget impacts derived from a model that has so many methodological problems – needs to be reflected more accurately in ICER's work, and specifically any financial projections or estimates should be as granular and relevant as possible so that they can be useful for individual health programs, payers, or groups of patients. Our very high-level recommendation on this last point is for ICER to either completely remove the "Potential Budget Impact" section of its reports, or to make them more relevant and useful by providing more specific projected financial implications for the major health financing sectors in the United States, e.g., Medicare, Medicaid, VA, DoD, commercial. In addition, for some new treatments and related interventions, it would also be appropriate to assess the spending implications for other programs or groups of providers, such as CDC and public health programs for a new treatment for an SDI, or hospitals and surgical centers for new antiseptics or antibiotics used in procedures.	We appreciate the desire to make ICER's budget impact analyses as granular and relevant as possible for "individual health programs, payers, or groups of patients." However, in a fragmented health care system such as that in the United States, the multiplicity of payers, provider organizations, and state and federal health programs would make such an exercise a major undertaking in itself, and would require the collection of data unique to each organization (and in some cases proprietary to those organizations). We believe that each of these organizations is better suited to judge the budgetary implications of new interventions for their particular populations and settings.