Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value

Public Comments on Draft Report

March 10, 2017

Contents

<u>AbbVie</u>
Abbvie's public comments on the Draft Evidence Report on Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value; Released January 20, 2017.

We welcome the opportunity to provide comments and suggestions where we believe there are opportunities to provide reader's with important and needed context, or strengthen the models themselves. Abbvie's suggestions are summarized into six main topics noted immediately below, followed by supporting information.

1. There is strong direct evidence supporting combination csDMARD-TIMs therapy over TIMs monotherapy.[7,8] We recommend including trials that directly compare monotherapy vs combination therapy, and conducting monotherapy and combination therapy as 2 distinct models.
2. The network meta-analysis (NMA) contains a group of highly heterogeneous studies for which the Bayesian random effects model cannot control for meaningful differences. We suggest that the authors reconsider their inclusion/exclusion criteria for the NMA and re-run the model.
3. We do not believe that the ADACTA study used in the NMA is applied correctly to the economic model or reflective of real world practice. Tocilizumab is demonstrated to have a clear dose-response relationship. The model assumes the efficacy of tocilizumab at its highest fixed dose of 8mg/kg, but applies costs only achievable at lower average dosing.
4. Inclusion of experimental treatments (baricitinib and sarilumab) is speculative and fraught with challenges to validity. We recommend excluding experimental treatments because dose and costs cannot be assumed.
5. The lifetime horizon with assumptions of fixed outcomes for csDMARD treated patients do not reflect the normal course of disease. We recommend conducting the model to account for intensification of therapy or decline of physical function. We recommend sensitivity analyses evaluating shorter time horizons.
6. Studies conducted in Asia may not generalize well to predominantly non-Asian North American populations.[1] We recommend that studies conducted solely in Asian countries be excluded from all analyses.

Section 4: General comments on the Comparative Clinical Effectiveness Network Meta-analysis:
A. <u>Systematic biases are not adequately discussed and addressed</u>
There are substantial limitations to the statistical modeling exercise that should be more explicitly addressed.

I. The biases introduced as a result of heterogeneity of study designs and patient characteristics cannot be overcome by the NMA's inclusion/exclusion criteria and Bayesian methodology.
   a. Pg 56, Fig 6: Systematic bias is introduced by the exclusion of trials which directly compare monotherapy vs. combination csDMARD-TIMs therapy. The NMA's modeling suggests that on average monotherapy is more efficacious than combination therapy. This conflicts with a large body of primary research[7], treatment guidelines[8], and product labeling.
   b. The selection criteria excludes a majority of clinical trials for some products and includes only clinical trials for others; producing substantial heterogeneity between products.
      i. Etanercept data are sourced from 3registries and 1 unblinded, non-inferiority study. This cohort of studies exhibit heterogeneity between etanercept populations[2], and vs the other products. The imbalance in study and patient characteristics for etanercept may explain the appearance of difference in average effect size for etanercept vs other TIMS (pg 56, Fig 6).

ii. Limiting certolizumab data to a sole study (ref #46) in the analysis may introduce bias and statistical imprecision in the effect estimate as reflected in Figure 6. Although excluded from the NMA, the EXXELERATE trial failed to show a significant benefit for CTZ over ADA in MTX inadequate responders.[14]

c. There is evidence that treatment response is different in Asian populations vs patients from US and Western Europe.[1] Based on this and that the main audience for this ICER review is US payers, we recommend excluding all trials solely conducted in Japanese/Korean populations as this introduces bias in favor of products that have data in this specific population.

II.   Random effects analyses should only be applied when the idea of a 'random' distribution of treatment effects can be justified.[3] Random distribution of treatment effects cannot be justified given the strong evidence of a dose-response effect for some TIMs, which is systematically different among the studies selected for the NMA.
   i. The NMA pools the results for infliximab using data from U.S. and non-US registries. Yet there is evidence that access to higher average doses in the US vs European countries is reflected in different clinical outcomes.[2] Therefore, treatment effects are not randomly distributed.

B. **Assumptions for experimental (unapproved) products introduces substantial uncertainty**
Neither baricitinib nor sarilumab are licensed for use in the U.S today. Each product has been studied with and without csDMARDs, and at varying dosages; with only their highest doses used in direct comparative studies vs adalimumab. It is presently unknown if the dose and concurrent csDMARD regimen used in the adalimumab comparative studies will be the same as that approved, nor if the dosage used in comparative studies will be used in the general population once licensed. If the products are approved, and lower doses are used in practice then the comparative effectiveness in real world practice cannot be assumed to reflect that of the clinical trials.

C. **Selection of end-points**
There are limitations in using the ACR scoring system to make indirect product comparisons which are generalizable to ICER's intended audience. While the ACR scoring instrument is appropriate for registration purposes, it is relatively insensitive in detecting differences between active treatments, and the ACR20 represents a low bar of clinical improvement. The American College of Rheumatology recognizes these and other limitations [4] and in response has proposed alternative measures to evaluate clinical outcomes in clinical practice.[5]

Section 6 General Comments (Long Term Cost-Effectiveness Model):
A. **Consequences for Remaining on csDMARD for moderate/severe patients over a lifetime are not included**
The lack of cost-effectiveness for any TIM over csDMARD therapy and relatively small difference in QALYs over a lifetime may be explained by the assumption that csDMARD patients maintain a consistent HAQ throughout the model. This assumption does not reflect the consequences of disease progression among moderate to severe RA patients who are not adequately controlled with a csDMARD alone. This lack of progression is unlikely as suggested by a significant reduction in the use of mechanical aids and devices since introduction of TIMs in the management of RA.[6]

Additionally, the most effective treatment to prevent structural damage progression is combination therapy with csDMARD + TIM.[7]

B. **Sensitivity analysis to evaluate impact of shorter time horizon for TIMs compared to Humira was not conducted**

The majority of US payors evaluate the impact of a drug over a shorter time-horizon. We recommend a sensitivity analysis be conducted to test the robustness of results comparing TIMs to adalimumab using a shorter timeframe.

C. **Biases on Cost Inputs**

There are several opportunities to improve the cost inputs within this model:

I. The systematic review is stated to be based on FDA labelled doses. For tocilizumab, the recommended starting dose is 4mg/kg, however, the dose used in all monotherapy trials referenced in the NMA evaluated a 8mg/kg starting dose. There are no studies directly comparing adalimumab to tocilizumab at the FDA approved starting dose for tocilizumab (4mg/kg). If efficacy inputs for the monotherapy model are based on this 8mg/kg dose, then the cost inputs should also reflect this dose. We appreciate the addition of dose escalation for some patients to 8mg/kg in the csDMARD+TIM as this is consistent with FDA product labeling and real-world use of this product.[5] However, we are aware of no evidence to suggest that doses less than 8mg/kg would achieved comparable outcomes to that suggested by the trial used to compare tocilizumab to adalumumab. We surmise that the ADACTA trial population of methotrexate intolerant patients is not generalizable to the real-world use of tocilizumab. ICER acknowledges descriptive analysis of real-world experience characterizing tocilizumab's dose and patient characteristics, but neglects to recognize that 95.8% of tocilizumab users are *biologic* experienced/failure patients.[12]

II. The exclusion of costs for products that require loading doses (eg, abatacept, certolizumab, golimumab, and infliximab) generates biases against products that do not require loading. We recommend that loading doses be incorporated into the costs for abatacept, certolizumab, golimumab, and infliximab.

III. The lab monitoring frequencies outlined generate biases in favor of tocilizumab and tofacitinib. There is no requirement for additional laboratory tests with adalimumab. Prescribing information for both tocilizumab and tofacitinib document increased monitoring compared to adalimumab as well as other TNF inhibitor therapies which should be reflected in cost inputs for this model. We recommend using FDA prescribing information for individual TIMs along with recommendations by the ACR[8] for additional monitoring requirements for csDMARDs in the csDMARD+TIM model. Monitoring for monotherapy should not require the same costs as for concomitant therapies.

IV. The inclusion of investigational products within the cost effectiveness models and budget impact models are speculative as the dose and costs are not available. The cost effectiveness results and budget impact analyses for both sarilumab and baricitinib depend upon assumptions of equivalent pricing with tocilizumab and tofacitinib, respectively. If they remain in the budget impact analyses, a sensitivity analysis should be conducted to include a variety of cost and dose assumptions.

Specific comments:

Page Number	Line Number	Comment on ICER statement or data in question
42/ 43	1-9 and 31-32	ICER Report States: **"***In one head-to-head trial, tofacitinib monotherapy produced better results in rates of clinical remission achieved, ACR response across all levels, and improvement in HAQ-DI and other patient reported outcomes compared with placebo, while differences between adalimumab monotherapy and placebo were not significant. Tofacitinib combination therapy was not statistically different from adalimumab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI in a second head-to head trial".* *"We identified two head-to-head studies of tofacitinib conducted in mostly TIM-naïve population. One study included both tofacitinib and adalimumab monotherapy arms, although the study was powered to detect differences between placebo and the two active arms and primary results were reported at 12 weeks.*[81] *Tofacitinib plus methotrexate was directly compared to adalimumab combination therapy in a second study".*[82] Pg 43, line 1-3 inaccurately states: *"Tofacitinib combination therapy was not statistically different from adalimumab combination therapy".* Recommend deleting this statement. <u>Response:</u> As stated in both study publications, neither study was designed or powered to directly compare adalimumab to tofacitinib. Therefore, no statement or inference should be made to imply statistical or comparative efficacy of tofacitinib vs adalimumab.
42-43/ 52- 54	31-32 for pg 42 and 1-8 pg 43/ Tables 4, 5, 7	Recommend excluding discussion on the Fleischman 2012 trial as this was an early Phase II, dose-ranging trial and based on outlined inclusion/exclusion it may not be appropriate to include the study. If it remains, ICER should include discussion of Study #81 to acknowledge that this trial is an outlier by not demonstrating significant efficacy of a positive control (adalimumab) vs pbo.
44	1-3	ICER States: *"Tofacitinib combination therapy was not statistically different from adalimumab combination therapy in rates of remission achieved, ACR response, and improvement in HAQ-DI in a second head-to head trial".* Comment: This is not a head to head trial, no statistical comparisons were made between the two active treatments. Therefore, if the study remains in the report this statement should be deleted.

44	29-31	ICER Statement: "*Compared with adalimumab combination therapy, the percentage of patients achieving an improvement greater or equal to the minimum clinically important difference threshold of 0.22 in HAQ-DI, was statistically-significantly higher in the baricitinib group (73% vs. 64%, p<0.05).*[84]" Response: Fair balance and discussion of clinical relevance is warranted with this statement. Even though the ***proportion achieving a minimally*** clinically important difference (MCID) was statistically different, we also observe that the mean difference in HAQ-DI was less than 0.22 at all time points[11]. The maximum difference between active treatments was approximately 0.15. Therefore it is unlikely that the small difference observed in this abstract would be clinically meaningful in clinical practice.
46	21-24	ICER Statement: "*Two additional trials compared adalimumab+methotrexate to either abatacept or tofacitinib combination therapy; neither trial detected discernible differences between TIMs in the proportion of patients achieving ACR20 or 50, although a significantly smaller proportion of patients achieved ACR70 with adalimumab in the tofacitinib study (10% vs. 20%; p≤0.01)*". Response: Again, the language as written inaccurately implies that adalimumab and tofacitinib were directly compared, and that the study was adequately designed and powered for a head to head comparison.
56	Fig 6	Recommend superscript citations for all treatments listed along Y-axis.
56	Fig 6	Adalimumab monotherapy is included in the graphic, but all 4 studies cited in the biobiography are studies of adalimumab *combination* therapy. Clear disclosure and attribution of data source(s) should be included.
58/ 142	4/ Table C13	The NMA for Sharp Score produces misleading results due to large differences in scores across csDMARD controls. Specifically, infliximab and etanercept are estimated to have the largest benefit, but it appears this result is driven entirely by the Sharp Score in the csDMARD arm of their trials being significantly worse than most other trials. Differences may be driven by variations in Sharp Score calculation (e.g., van der Heijde, modified van der Heijde, vs. Genant) or patient populations. Differences should be investigated and trials should be excluded if necessary.
59	Table 10	More information on how the adverse event rates in Table 10 were calculated (and which trials contributed evidence) would be appreciated.
126	Table C3	In column 1, adalimumab is cited to have **4** studies included (ref #159-159). But in column 8, the authors state that **5** RCTs are included. Recommend the difference be reconciled, and a check be done to see which studies were included in the analysis.
131	Fig C1	Network diagram for analysis of ACR. The diagram has no linkage to the specific studies used to create the network. Would recommend adding the citations to the diagram.
81	5 and6	There is a statement that cost-effectiveness was improved with monotherapy over combination therapy. This is not consistent with clinical

		data showing superior outcomes with MTX-combination therapy over monotherapy.
170	Table D1	The frequency of monitoring should be taken directly from US FDA Prescribing information. Additionally, the ACR guidelines recommend that any TIM given in combination with MTX or other csDMARDs require additional monitoring, however when the TIM is given as monotherapy, monitoring frequency should be based on prescribing information.[8] The monitoring frequency for adalimumab described in Table D1 incorrectly states that 1 annual office visit and TB test, and 4 liver labs and blood tests are required. **<u>Per Humira FDA prescribing information, there is no requirement for additional liver/blood tests while on treatment.</u>** The information in D1 is not consistent with prescribing information for tocilizumab and tofacitinib package inserts. **Both Xeljanz and Actemra FDA prescribing information support more laboratory monitoring vs. the Humira label and this is not reflected in Table D1**. For the monitoring costs, there is no mention of a lipid panel which is not tested in a CBC (ie, blood lab). We recommend that this be added. Assumption that baricitinib will have the same monitoring requirements as tofacitinib may prove untrue.

Supporting Citations:

(1) Takeuchi T, Kameda H. Nat Rev Rheumatol. 2010;6(11):644-52.

(2) Greenberg JD, Reed G, Decktor D, et al. A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry. *Annals of the rheumatic diseases.* 2012;71(7):1134-1142.

(3) The Cochrane Handbook Cochrane Handbook for Systematic Reviews of Interventions 4.2.5.

(4) AMERICAN COLLEGE OF RHEUMATOLOGY COMMITTEE TO REEVALUATE IMPROVEMENT CRITERIA. Arthritis & Rheumatism (Arthritis Care & Research) Vol. 57, No. 2, March 15, 2007, pp 193–202. http://www.rheumatology.org/Portals/0/Files/A%20Proposed%20Revision%20to%20the%20ACR20.pdf

(5) Anderson J., et.al. Rheumatoid Arthritis Disease Activity Measures: American College of Rheumatology. Recommendations for Use in Clinical Practice. Arthritis Care & Research Vol. 64, No. 5, May 2012, pp 640–647. DOI 10.1002/acr.21649.

(6) Strand V, et al. Impact of treatment with biologic agents on the use of mechanical devices among rheumatoid arthritis patients in a large US registry. Arth Care Res. 2015;68(7):914-21.

(7) Goekoop-Ruiterman YPM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis & Rheumatology. 2005;52(11):3381-90.

(8) Singh J, et.al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid ArthritisArthritis Care & Research Vol. 68, No. 1, January 2016, pp 1–25.

(9) THU0126 Added-Value of Combining Methotrexate with a Biological Agent Compared to Biological Monotherapy in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Randomised Trials

(10) Jørgensen, T S, et.al. THU0126 Added-Value of Combining Methotrexate with a Biological Agent Compared to Biological Monotherapy in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Randomised Trials Conference Paper in Annals of the Rheumatic Diseases 74(Suppl 2):239.3-240 · June 2015. DOI: 10.1136/annrheumdis-2015-eular.3396.

(11) Keystone E., et.al. Baricitinib versus placebo or adalimumab in patients with active rheumatoid arthritis and an inadequate response to background methotrexate therapy. EULAR Poster THU0609 2016 (Fig 3).

(12) Pappas D. et.al. Dosing of Intravenous Tocilizumab in a Real-World Setting of Rheumatoid Arthritis: Analyses from the Corrona Registry. Rheumatol Ther (2016) 3:103–115

(13) Gabay, Cem et al.Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial The Lancet;381(9877):1541 – 1550.

(14) Smolen J, et.al. Head-to-head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomized EXXELERATE study. Lancet 2016;(388):2773-2774.

Aimed Alliance
February 17, 2016

Steven Pearson, MD
Institute for Clinical and Economic Review
2 Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Alliance for the Adoption of Innovations in Medicine (Aimed Alliance) is a nonprofit organization that improves health care in the United States by expanding access to treatments and technologies. On behalf of Aimed Alliance, I respectfully submit the following comment in response to the Draft Evidence Report, entitled "Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value: Draft Evidence Report" ("Draft Report") published by the Institute for Clinical and Economic Review ("ICER").

Rheumatoid Arthritis ("RA") is a chronic inflammatory disease that affects approximately 1.5 million people in the United States.[1] RA is primarily a disease of the joints, resulting in pain, swelling, stiffness, and loss of function.[2] Yet, it can also affect individuals' mental health, causing depression, anxiety, feelings of helplessness, and low self-esteem.[3] RA can interfere with nearly every aspect of an individual's life, from work to family life, including impacting the decision of whether to have children.[4] To control symptoms, prevent relapse and disease progression, and improve overall quality of life, individuals with RA must have access to effective treatment options. However, we fear that the Draft Report will limit those options.

QALYs are Discriminatory

Aimed Alliance appreciates ICER's inclusion of life years gained to measure the benefits of RA medications. However, the use of quality-adjusted life-years ("QALYs") to develop a rigid price cap is inconsistent with American values and public policy. Congress added language to the Patient Protection and Affordable Care Act that prohibited the Patient-Centered Outcomes Research Institute ("PCORI") from using QALYs as a threshold for determining coverage, reimbursement, or incentives in the Medicare program. The ban reflected a long-standing concern that the approach would lead to health care rationing as well as age- and health status-based discrimination, unfairly favoring younger and healthier populations.

QALYs put a price tag on the value of a human life that merely reflects an individual's diagnosis and deems those with chronic, debilitating, and rare conditions, such as RA, as being worth less than the rest of the population. They treat individuals' lives and health as a commodity and ignore the patients' and practitioners' individualized concept of the value of treatment. Therefore, the QALY should not be used

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[1] *Handout on Health: Rheumatoid Arthritis*, National Institute of Arthritis and Musculoskeletal and Skin Disease (Feb. 2016), https://www.niams.nih.gov/health_info/Rheumatic_Disease/#ra_2.
[2] *Id.*
[3] *Id.*
[4] *Id.*

to set a threshold for a large population of individuals with one-of-a-kind life narratives across a complicated health care system.

Prioritizing Access to Options

The Draft Report acknowledges that all eleven targeted immune modulators ("TIMs") significantly improve survival, disease activity, remission, and other key outcomes as compared with disease-modifying anti-rheumatic drug ("DMARD") therapies alone. Although each TIM added approximately 17 life years when added on to DMARD therapies, the Draft Report suggests that TIMs are not cost-effective. This conclusion does not follow and could lead to restrictions on access.

To ensure patients receive adequate care, quality and choice of treatment options should not, by default, be sacrificed for cost-saving measures. The United States Court of Appeals for the Ninth Circuit has stated that "[f]aced with such a conflict between financial concerns and human suffering . . . the balance of hardships tips decidedly in [the patients'] favor."[5]

Prior to the availability of TIMs, individuals with RA suffered long-term damage to their joints and irreparable damage to their entire bodies, leaving them debilitated, immobilized, and in persistent pain. Many patients would argue that the benefit of reducing or altogether eliminating such damage far outweighs the cost of the medications. In fact, a recent poll conducted by Aimed Alliance showed that Americans are willing to pay more for innovative treatments for themselves and their loved ones to live longer and prevent unnecessary pain and suffering.[6]

As ICER simultaneously acknowledges and dismisses, the American College of Rheumatology ("ACR") recommends that individuals with RA need individualized treatment in order to lower disease activity and achieve remission.[7] The ACR, therefore, recommends more aggressive drug treatment of RA while still in its early stages.[8] As such, the value of each RA drug must be made at the patient level, on a case-by-case basis.

Patient 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.

Although ICER consulted with patients and patient groups on the topic of moderate-to-severe RA, it is unclear how ICER incorporated patient feedback. Given the significant improvement on the quality of life that TIMs provide, it seems highly unlikely that patients and patient advocates would deem the entire class of drugs to be not cost effective. Moreover, while patient advocacy groups noted that step therapy and prior authorization are a major barrier to proper care and source of anxiety for patients,

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[5] Lopez v. Heckler, 713 F.2d 1432, 1437 (9th Cir. 1983).

[6] *Aimed Alliance Poll: Principles for U.S. Health Care*, Aimed Alliance (Dec. 15, 2016), http://www.aimedalliance.org/wp-content/uploads/2016/12/Aimed-Alliance-Principles-for-U.S.-Health-Care-Poll.pdf.

[7] *Rheumatoid Arthritis*, University of Maryland Medical Center (Mar. 18, 2013), http://umm.edu/health/medical/reports/articles/rheumatoid-arthritis.

[8] *Id.*

suggestions that TIMs are not cost-effective would serve to bolster third-party payers' use of such policies in direct conflict with patients' best interest.

Faulty Assumption

Finally, in making its calculations, ICER assumes that patients switch medications due to lack of effectiveness or occurrence of adverse events. In making this assumption, ICER ignores that patients are often switched due to nonmedical switching. Nonmedical switching occurs when an insurer requires a stable patient to switch from his or her current, effective medication to a cheaper, alternative drug.[9] The change occurs as the result of the insurer dropping a medication from the formulary altogether, moving a drug to a higher cost tier, or increasing the out-of-pocket costs owed after the plan year has begun. Nonmedical switching is done without consideration of the medical repercussions or reasoning behind the prescriber's selection of the original medication, and often without the prescriber's knowledge.[10] Additionally, when a patient signs up for a new plan, he or she may have to start the step-therapy process over again before accessing his or her preferred medication.

Such switches can result in the patient receiving ineffective treatment and experiencing a relapse or progression. Therefore, not only do we caution against using assessments based on cost-savings alone, especially for stable patients, but we discourage making the assumption that switches are based on ineffectiveness of treatment or occurrence of adverse events when calculating the value of a treatment.

Conclusion

Thank you for your consideration regarding the Draft Report, and 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 Report.

Respectfully submitted,

Stacey L. Worthy
Executive Director

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[9] *Keeping Stable Patients on Their Medications*, Coal. of State Rheumatology Organizations, http://www.csro.info/Switching (last visited Jan. 14, 2016).
[10] *Id.*

February 17, 2017

Steven Pearson, MD
President, Institute for Clinical and Economic Review
Boston, MA 02109 USA

Re: Institute for Clinical and Economic Review (ICER) Review of Treatments for Rheumatoid Arthritis

Dear Dr. Pearson:

The American College of Rheumatology (ACR), representing over 9,500 rheumatologists and health professionals, appreciates the opportunity to respond to ICER's draft evidence report on the review of treatments for rheumatoid arthritis (RA). We appreciate ICER addressing this important topic and would like to share our reflections, questions, and concerns about ICER's approach, methodology, and conclusions of the report.

The ACR is an active supporter of comparative effectiveness research (CER) that can inform physician and patient decisions about treatments. CER has the potential to enhance understanding of the pros and cons of different treatment options. In the best case scenario, CER would highlight the need for multiple treatment options to address heterogeneous groups of patients. However, conclusions that are drawn without taking into consideration long-term data and heterogeneity of patient population across unique blend of co-morbidities and preferences and tolerances must be considered within their limitations. The ACR is concerned that the ICER report, while based on an acceptable method of cost-effectiveness analysis, does not provide sufficient data on model structure and validation.

We are concerned about the lack of clarity regarding the comparator strategy of combination DMARDs. All assumptions related to the comparator arm (cDMARDs) have not been clearly outlined in the report. After review of the report, some key questions remain. For example, if the analysis starts from the time of DMARD failure and lack of ACR response, what are the treatment options in the absence of biologics? How has the natural history of disease progression been incorporated in the model? For example, failure to initiate effective strategies after an inadequate response to cDMARDs would be expected to lead to further decrease in the HAQ scores (1.45 average vs 1.7 at the model entry). These concerns raised questions about whether the model adequately captures long term outcomes in persons who fail to respond to DMARDs.

The 2nd Panel on Cost-Effectiveness in Heath and Medicine recommends that external model validation should be an integral part of cost effective analysis. We were unable to find the evidence

of the external model validation in the report and would like to request that ICER provide full details of the model (an excel file) and validation of the model-based outputs (such

as 5-year survival, 5-year cumulative rate of hospitalization, and cumulative rates of cardiovascular events and HAQ trajectories) by comparing them with external data from large longitudinal registries. External validation is critical prior in order to evaluate whether the model's predictions are reflective of the RA population in the US.

The ACR appreciates that the ICER report has confirmed the important clinical impact of biologic therapies for RA patients and we are cognizant that these are expensive medications. However, we are surprised that the sensitivity analyses did not address the cardinal parameter; the cost of the biologics. We believe that such sensitivity analyses are required to provide key stakeholders data on how varying cost-thresholds would impact the cost effectiveness of biologics. It would be immensely helpful to focus the report on how to make these effective treatments cost-effective and affordable. We are concerned that the ICER report, which is based on a limited set of assumptions, will limit effective treatment for RA patients for whom there are no alternatives. Ample data have shown that this scenario leads to higher rates of irreversible joint damage and disability. More extensive sensitivity analyses suggesting parameter thresholds that would make the biologics cost-effective, taking into consideration the heterogeneity of RA patients, would make this report more actionable.
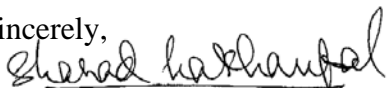
We appreciate ICER's focus on randomized clinical trial data and agree that it presents the highest level of evidence; however, our concern is that most of trials provide only short-term data on drug efficacy and do not adequately reflect the numerous treatment changes required to control RA in clinical practice.

In addition, it is unclear whether rheumatologist content experts participated in model development or just were given a report to provide the feedback. A better description of the roles played by the clinical advisors would be helpful. While several rheumatologists were listed on the report, it is not clear whether those individuals were primarily used in an advisory capacity or were a part of the model development team. Using rheumatologists in an advisory capacity allows limited ability to provide meaningful input. ACR has found ICER very willing to speak with interested stakeholders, but question the level of meaningful impact stakeholder input has had on the report.

The report also does not include transparent disclosure information from the members of the ICER team or reviewers as well as funding sources that supported the work, which are critical when publishing scientific reports that are meant to impact care.

We appreciate ICER undertaking this important work and believe more work is needed to help address the important issue of treatment of patients with RA. The ACR appreciates the opportunity to respond to this report. Please contact Rachel Myslinski, Vice President of Practice, Advocacy and Quality at ███████████████████████████ if you have questions or if we can be of assistance.

Sincerely,

Sharad Lakhanpal, MD
President, American College of Rheumatology

Amgen Response to ICER Rheumatoid Arthritis Draft Evidence Report

Amgen is a science-based company committed to developing and delivering innovative medicines. As part of our mission is to serve patients, we appreciate the opportunity to comment on the ICER Draft Report "Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value" in patients with rheumatoid arthritis (RA) who have inadequate response to conventional disease modifying anti-rheumatic drugs (cDMARDs).

The ICER model fails to incorporate evidence from over 20 years of real-world use of targeted immune modulators (TIMs). The main premise of the ICER model is to estimate the value of TIMs, in patients who have had an inadequate response to cDMARD therapy in real-world practice. As the result of flawed assumptions and methodologic issues, the ICER model overestimates the treatment effect of continued cDMARD therapy in a way that belies the severity of the disease and contradicts years of observational evidence cataloging the devastation of long-term, uncontrolled RA.[1,2] To correct this, ICER should adjust treatment effect (eg, Health Assessment Questionnaire [HAQ] scores) using observational data to account for disease progression on cDMARDs. Methodologically, ICER should adopt a patient-level modelling approach and use improved methods to estimate long-term utility to account for patient characteristics and treatment variability.

To produce a meaningful and clinically relevant model, Amgen strongly recommends that ICER correct the flawed assumptions and methodologic issues associated with the current model. The following changes would more appropriately model the effect of TIMs in a population whose disease is inadequately controlled with cDMARDs:

1. Incorporate evidence that best represents the long-term clinical and patient outcomes from over 20 years of real-world use
   a. Evaluate the trajectory of HAQ scores appropriately for cDMARDs
   b. Incorporate treatment sequences with multiple changes that reflect clinical practice
2. Use the disease appropriate individual patient-level simulation model to address patient differences and uncertainty in the base case
   a. Account for RA population variability
   b. Adjust treatment discontinuation rates
3. Estimate utilities based on the mixture model approach

Incorporate evidence that best represents the long-term clinical and patient outcomes from over 20 years of real-world use

The benefits of cDMARDs are overestimated when clinical trial data are extrapolated over a lifetime horizon without accounting for the disease progression that occurs in patients whose RA is inadequately controlled with cDMARDs.[3-5]

The ICER model assumes that patients with moderate-to-severe RA achieve a consistent lifetime benefit on cDMARDs. As noted in ICER Table 8 reporting the network meta-analysis (NMA) derived populations, only 27% of inadequate cDMARD responders achieve an ACR 20 in the "second-chance" clinical trial setting. This low response is compounded further by the discontinuation of these therapies in real-world situations with about half the patients treated with methotrexate discontinuing therapy within 12 months.[6] Thus, the evidence does not justify the ICER assumption that these patients would achieve a consistent lifetime benefit on cDMARDs.

Instead of relying on clinical trial data, the ICER model should account for long-term outcomes and disability in patients with RA by using observational data.

Evaluate the trajectory of HAQ scores appropriately for cDMARDs

The ICER model uses fixed HAQ scores over time after cDMARD treatment. This demonstrates one serious limitation of using short-term data to assess the value of TIMs relative to cDMARDs.

Real-world observational studies suggest that HAQ outcomes vary by treatment and that HAQ scores deteriorate with long-term cDMARD therapy.[7,8] As HAQ scores are used to derive utility outcomes, the assumption that HAQ scores do not change in the ICER model leads to an overestimation of the utilities, quality-adjusted life years (QALYs), and overall value of cDMARD therapy.

ICER should adjust HAQ scores for long-term cDMARD therapy based on real-world data.

Incorporate treatment sequences with multiple changes that reflect clinical practice

The treatment sequences implemented in the ICER economic model do not reflect those used in clinical practice and consequently could mislead payers on the true cost effectiveness of TIMs utilization, leading to patient access concerns.

Insights gained from physicians, patients, and patient groups affirm that "it is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate" (ICER report p17). Given that many treatment changes occur in the course of RA patient management, the ICER model should better account for the number of lifetime drug sequences and switches that can occur as well as the challenges of evaluating individual therapies.

ICER should examine US RA registries like CORRONA, RISE, or National Data Bank to identify the most common sequences of TIMs used in clinical practice. Data from these sources also provide real-world estimates of drug discontinuation due to switching agents or stopping therapy because of lack of response or intolerance.

ICER should include additional sequences of TIMs (ie, at least 2 TNF inhibitors plus one of each of the other classes) rather than converting to cDMARD palliative therapy following the failure of three TIMs (ICER report p71).

Use the disease appropriate individual patient-level simulation model to address patient differences and uncertainty in the base case

Account for RA population variability

The ICER economic model uses a rigid cohort approach that inappropriately assumes a homogeneous RA population (ICER report p86). This model is severely limited by not accounting for future outcomes influenced by patient history or individual patient characteristics.

The ICER base case analysis should include the following important factors: treatment history, the effects of patient characteristics on utilities, and treatment discontinuation rates. For example, the probability of a patient switching to the next TIM must depend on the number of previous TIMs the patient failed. In addition, lifetime QALYs are larger for younger patients because they have more potential life years; comorbid conditions such as cardiovascular disease and diabetes degrade HAQ scores.[7] It is not possible to include such assumptions with the cohort model currently used by ICER.

Adjust treatment discontinuation rates

The ICER base case analysis does not adjust discontinuation rates based on patient response (ICER report p70). The reasoning is flawed as patients with lower response levels have higher rates of treatment discontinuation.[9] Furthermore, the ICER base case analysis assumes that patients only discontinue treatment due to adverse events. In reality, patients stop treatment for many reasons, including lack of adequate clinical response, so only using adverse events to estimate discontinuation

overestimates time on treatment. The model should incorporate treatment discontinuation from "all cause" and estimate the probability of discontinuation due to an adverse event or other reason.

A patient-level simulation model is common in RA analyses due to patient heterogeneity, the variability in treatment sequences, and uncertainty in treatment effects and duration.[9,10] ICER should use a patient-level simulation model to capture the patient complexity and the variability and uncertainty associated with treatment in clinical practice.

Estimate utilities based on the mixture model approach

The ICER model does not appropriately degrade HAQ scores in patients whose RA is inadequately controlled with cDMARD therapy.

In most RA models, including the ICER economic model, the utility estimation is the central predictor of QALY outcomes. The HAQ score is the primary variable in the RA utility algorithm and is used to estimate hospitalizations, mortality, and costs. As HAQ scores are only available in a few clinical trials, the ICER model calculates HAQ scores using ACR scores and modified Total Sharp Scores (mTSS) sourced from short-term clinical trials. The ACR scores and mTSS are inputted into various equations to estimate the long-term HAQ scores and QALY outcomes.

Without direct clinical trial estimates of HAQ scores, it is important to use the best available method to estimate utilities. The HAQ-utility algorithm used in the ICER model is out of date and does not properly predict the distribution of utility scores.[11] A recently published algorithm based on the mixture model to translate HAQ scores to patient utility has better predictive accuracy than previous algorithms.[12-14]

Given that different algorithms convert HAQ score to different utility values, possibly leading to different QALY and cost-effectiveness results,[15] we recommend that ICER use the mixture model algorithm,[12-14] which we believe is the best performing algorithm for estimating utilities.

Concluding remarks

The ICER RA Draft Report fails to fully capture the value of TIMs by using an outdated, one-size-fits-all economic model that relies too heavily on short-term controlled clinical trial data that fail to capture real-world patient-specific impacts. This approach greatly underestimates the disability (that can take years to develop) associated with untreated or undertreated RA. The ICER model overestimates the effectiveness of cDMARDs on maintaining good disease control, uses treatment sequences that fail to reflect clinical practice, does not acknowledge individual patient differences in its simulation, and uses fixed HAQ scores that do not adequately account for observed degradation of patient functioning over time. As a result of these flawed assumptions and extrapolations, the ICER model leads to an overstated cost per QALY for cDMARDs and an undervaluation of TIMs.

When evaluating TIMs, ICER has a responsibility to incorporate the totality of evidence, costs, and patient/societal perspective in a highly transparent and credible manner. As currently presented, the ICER analysis fails to reinforce the importance of preserving patient treatment choice across all RA treatments based on individual patient needs, specific disease characteristics, clinical expertise, and patient preference. When patients with moderate-to-severe RA lack access to effective and well-tolerated treatments, they experience lifelong disability.

ICER should correct the flawed assumptions and methodologic issues highlighted above to produce a meaningful and clinically relevant patient-centric model.

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<u>Anthem</u>

February 17th, 2016

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

Re: ICER Releases Draft Evidence Report on Treatments for Rheumatoid Arthritis

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 73 million people served by its affiliated companies, including nearly 40 million enrolled in its family of health plans. For more information about Anthem's family of companies, please visit www.antheminc.com/companies.

In Anthem's role as a payer we share Institute for Clinical and Economic Review's (ICER's) commitment to researching and evaluating drugs 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 drug therapies – such as those intended to treat rheumatoid arthritis. In response to ICER's draft Evidence Report on Treatments for Rheumatoid Arthritis, Anthem would like to share several high-level comments:

- **Limitations associated with the modeling of investigational (non-FDA approved) drugs.** – Unknowns regarding long-term efficacy and safety are two important limitations which should be clearly noted with the modeling of investigational, non-FDA approved drugs. Furthermore, similar caveats should be properly noted regarding newer-to-market therapies, given that clinical experience remains limited. Similarly, generalizability to populations not specifically evaluated in clinical trials must be duly noted as the population treated and clinical experience expands as more precise estimates comes to fruition.
- **The difficulty associated with assessing and balancing adverse events and/or safety issues in ICER models**.
- **Step therapy requirements employed by payers (e.g. conventional DMARD, TNFα inhibitors) do not necessarily reflect economic considerations, but may be based on clinical concerns -** For example, step therapy requirements may be based on the clinical trial inclusion criteria used to evaluate the therapy, or they may be based on balancing the safety unknowns of newer therapies versus those of already well-established therapies.

We strongly encourage organizations like ICER to an ongoing value assessment of rheumatoid arthritis treatments for new market entries to ensure that these drugs (both brand and generic) are not resetting the market in a way that causes untenable cost burdens on patients and payers (both public and private).

<div align="center">***</div>

We look forward to working with you as you move through the review process.   Should you have any questions or wish to discuss our comments further, please contact ███████████████████████ ███.

Sincerely,

Geoffrey B. Crawford, MD, MS
Medical Director – Clinical Pharmacy & Medical Policy

<u>**Arthritis Foundation**</u>
February 17, 2017

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

RE: Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value Draft Evidence Report

Dear Dr. Pearson,

On behalf of the more than 1.5 million adults in the United States with doctor-diagnosed rheumatoid arthritis (RA), the Arthritis Foundation is pleased to provide comments to the Institute for Clinical and Economic Review (ICER) on *Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value Draft Evidence Report.* First, we appreciate the working relationship the Arthritis Foundation has had throughout this process with ICER and your engagement with patients and stakeholders in the evidence report development process. Highlighting the complex nature of treating RA patients is vitally important to this review process. Please find our specific comments on the draft evidence report in the subsequent sections.

Stakeholder Input. In our many conversations, we have agreed that RA is a complex disease that requires nuanced treatment, unique to each person suffering from this disease. An RA diagnosis not only affects the person's quality of life, but is known to impact their entire family. We continue to believe stakeholder input, including that of caregivers, is critical if ICER is to have a comprehensive understanding of the disease. We applaud ICER for the inclusion of a patient, caregiver, and provider panel that will also provide input during the public meeting. We look forward to revisions of the ICER methodology that will address issues inherent to the current process. Notably we are pleased to see in recent ICER announcements, the calculation of prices as net of rebates and discounting rather than relying exclusively on Wholesale Acquisition Cost (WAC).

Timeline. We appreciate the revisions of ICER's review timeline to allow for stakeholder input. However, we remain concerned that the comment deadlines and time for engagement with ICER are too short for many patient and provider groups, given the volume of information necessary to respond. We urge ICER to continue to re-evaluate the processes and timelines given the limitations of the patient advocacy and provider communities to quickly provide feedback. Allowing more time for comments and engagement would also provide more comprehensive input from various stakeholders.

Executive Summary. While we understand the current report is not final, the Arthritis Foundation believes we were unable to make comments on the entirety of the document due to the absence of an executive summary. We urge ICER to present a draft executive summary in future reviews so stakeholders can understand how conclusions will be presented and provide additional comments that could inform the interpretation of the results.

Background. We appreciate ICER conducting a broad literature review. Unfortunately, there are vast gaps in the current literature surrounding RA medications and clinical trials. It is very concerning that there are limited long-term studies regarding the natural occurrence of RA or innovative RA

medications, indicating potential underreporting of outcomes, adverse events, and safety concerns[i]. RA patients may be switched between medications frequently, but these changes are only reported administratively. Therefore, the reasons for prescribing patterns are largely unknown. In order to ascertain clinical intent for changes in treatment, more robust data sources are needed[ii]. Many of the clinical trials conducted for RA are not with random populations and tend to be homogenous in nature. As a result, many populations may be under-represented. For example, patients with early or mild RA who are otherwise healthy and have infrequent visits to their doctor are under-sampled[iii]. It is extremely important to appreciate cases of earlier onset RA, because the first two years are a critical time when the patient is most susceptible to irreversible structural damage. As examined below, the short duration of clinical trials relative to the course of disease may be insufficient to fully capture positive outcomes realized by patients over longer periods of treatment.

In general, we feel the report's survey of the disease background is sparse. We recommend ICER add additional references throughout the entire report. This is particularly important in background information surrounding the field of Cost Effectiveness (CE) research. ICER's results are not fully contextualized with other attempts at CE in RA. We also continue to encourage ICER to edit the document for any misleading wording. For example, we encourage clarity on language around rare patient cases and drug usage. In these instances, careful attention should be paid to assuring that rarity is not used to suggest that the cases should be disregarded as an aspect of future policy decisions. We also seek elaboration on biosimilar treatment information included in the review. It is unclear in the report whether biosimilar clinical data is limited only to trials that specifically tested the biosimilar, or whether the definition of biosimilarity allowed ICER to consider clinical data of reference molecules to be considered in the analysis of the biosimilar. Pricing of both reference molecules and biosimilars remains uncertain and factors prominently in the ICER conclusions. As the debate on pricing evolves, it will be important to appropriately assign available clinical data to each molecule.

The Topic in Context. The population of interest includes adults ages 18 and older with most of the included population aged 55-65 with moderate to severely active RA and inadequate responses to or intolerance of conventional disease modifying anti-rheumatic drugs (cDMARDs). We feel this population limitation is a significant flaw in ICER's report. We believe the report will vastly underrepresent the total RA patient population. If patients with early diagnosed to mild RA were included in the economic model, we would expect the population treated with targeted immune modulators (TIMs) to accrue greater additional quality adjusted life years (QALYs) compared to those who remain on methotrexate alone. The target population as described is likely enriched for patients who have had the disease for longer periods of time, and stand to realize fewer QALYs. Table c17, for example, reports only one study included in which mean disease duration was less than 2 years.

Second, while a definition of base case is not readily evident in the report, it appears that the base case age is approximately 60 years old. RA is well reported to reduce life expectancy of men and women by 5-10 years, and this provides a separate design flaw. In this case, the target population will have a shorter lifetime experience with the disease, and will realize fewer QALYs as a result. This apparent statistical right censoring of the age data has other features that impede claims of representativeness. Available data suggest that TIMs effectiveness increases over time, whereas cDMARDs in DMARD inadequate responders get worse. We reiterate, effectiveness may increase over time, in a way that is not fully captured within ICER's current model.

Without an analysis to address representativeness of the target population, the ICER report must be considered limited as an academic contribution. This is, however, not only an academic publication, but

rather a powerful driver of policy. In this draft version, an inattention to representativeness makes this document wholly inappropriate for consideration as a primary influencer of health policy. We urge ICER to better represent the target population by including younger patients and those diagnosed with early/mild RA as part of the target population. Further, we request that an analysis of a broader target group be provided in the main analysis. If inconclusive, we feel strongly that any results obtained in the narrower age group be accompanied by sensitivity analyses that focus on base case age, time since initial diagnosis, base case QALYs, treatment efficacy, and pricing on cDMARD alone or after cDMARD failure. With regard to data presented in Table 15, the report of QALYs attributable to TIMs or cDMARDs does not express the variability of the efficacy of either group. We have concerns regarding DMARD failure where TIMS generally doubled American College of Rheumatology response criteria (ACR20/50/70) effectiveness (e.g., SATORI trial). We thus request that sensitivity tests be included to test values along the variances reported in the studies. The Arthritis Foundation continues to have concerns regarding the citation of Rhor (2016). This paper includes a disclosure that it and its authors were financially sponsored by a company that would stand to benefit from the claims ICER has used this paper to support. We further ask that if these claims cannot be supported by additional studies, that the potential conflict of interest be acknowledged in the ICER report.

Comparative Clinical Effectiveness. In the report, ICER makes conclusions based on the ACR response criteria (ACR20/50/70). The Arthritis Foundation recommends avoiding conclusions based on ACR20 in dose escalation studies, per the Food and Drug Administration (FDA) guidance. ACR20 is an insensitive score, and does not perform as well as the Disease Activity Score with 28-Joint Counts (DAS28) or other more sensitive measures in this analysis. We direct attention to ACR20 reported in Table 9, which reports 77% ACR20 for cDMARD, whereas Figure 6 suggests an ACR20 of 26.9%. These differences should be clarified. In larger perspective, attention should be given to the limits of the ACR20, including issues related to thresholds at which clinically significant improvements can be defined[iv].

Similarly, we recommend Sharp Score data be eliminated from the analysis. Observer variability is high, and there is little prognostic value of the score with respect to outcomes such as joint replacement and work function. Notably, Table 9 of the report notes insufficiency of Sharp data to compare TIM experienced populations. In regard to *Table 12-Evidence Ratings*, we suggest providing a range around which the rating is judged with a presentation of confidence, given the limitations expressed in the paragraphs prior. We encourage ICER to include an additional section providing other algorithms that have been used to estimate comparisons, such as those employed in the United Kingdom, Australia, or available in US based academic literature. It would be beneficial to see these studies cited, and the difference between those results and ICER's. The Arthritis Foundation believes ICER's economic model is a work in progress and should not be considered final. We urge ICER to update their modeling to include real world evidence (RWE) as well as measures for people who fail cDMARDs and TIMs showing that their disease worsens over time. We also seek clarity on the processes that ICER has or will develop to update all reports.

Other Benefits or Disadvantages. In regard to the QALY measures used, there is a strong argument that QALYs measured on short-term (often reversible) symptoms do not adequately predict QALYs on longer (2+year) studies. In longer studies irreversible structural damage can be factored into the calculation, and has greater bearing on Health Assessment Questionnaire Disability Index (HAQ-DI). We believe this is a fundamentally important concept as it differentiates symptoms like pain and swelling (measurable in near terms), from functionally compromised joints (which require longer surveillance). We urge ICER to run an analysis of QALYs determined in studies lasting greater than >2

years to see if QALYs associated with any intervention differ from estimates favoring shorter studies. In doing so, ICER may find QALY outcomes beneath the $150,000 threshold of acceptability. Given the differences between the measured QALY and patient sentiment as to the value of these medications, more work to understand this difference of opinion is warranted. As ICER continues to refine this section of their modeling, we ask that ICER recognize that no single QALY threshold estimate can or should be generalizable to all populations, and that QALY thresholds vary by decision-maker, population, and disease. We also ask that ICER expand on their QALY methodology and acknowledge the degree to which uncertainty is present in their conclusions.

Further, we continue to seek clarity on the inclusion of comorbidities in the model. Many patients with arthritis also suffer with comorbidities such as cardiovascular disease, mental health conditions, infections, and malignancies[v]. Of adults diagnosed with arthritis, 47% also have at least one of the previously listed conditions and as many as 40% of people with rheumatoid arthritis (RA) experience significant symptoms of depression[vi]. These symptoms can lead to more physical function problems, higher disease activity, physical and social inactivity, poorer health overall, and an increased need for medical care[vii]. We urge ICER to revise and incorporate how comorbidities are accounted for in the incremental costs outcome measures.

Long-Term Cost-Effectiveness. As previously stated, we believe a glaring issue in the long term cost effectiveness section is the misrepresentation of patients who fail all TIMs and stay with cDMARD, or no drug therapy for the rest of their lives. The current model assumes that people do not get worse over time without effective treatment, contrary to research. We also remain concerned that patients older or younger than the inclusion criteria are not adequately represented. There is ample evidence to suggest treatment differences and differences in the overall patient experience. Additionally, due to the nature of their insurance, these patients may also differ from those included in the report. We hope that ICER will consider these factors in the final report and subsequent reports on other disease states.
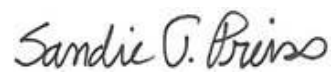
Overall, keeping patients stable on the right medication is critical to maintaining positive health outcomes and greater productivity for patients. We worry that there are parts of ICER's modeling that could threaten a medically stable patient or limit treatment options for patients. The Arthritis Foundation fights to ensure people with arthritis have timely access to the medications they need to function in daily life. We believe attempting to make decisions about the value of a drug without broad-based robust supporting data from patients and providers who are in daily contact with patients is a questionable practice. We ask that the report make mention of the importance of the patient and prescriber relationship in choosing the appropriate treatment for RA patients. We also ask that ICER consider its current process to evaluate and make decisions regarding new treatments. As new treatments and additional information about these treatments become available, we urge ICER to consider publishing a protocol for how these reports will be revised in the future. Further, we ask that ICER develop a patient friendly summary of the reports at the end of each review. Summaries should be concise and easily understood by a patient; we welcome the opportunity to work with ICER on creating a patient-friendly tool.

Finally, the Arthritis Foundation cannot support any recommendations that limit patient access to needed therapies or could result in a patient on a stable drug no longer having access to that drug. We remain confident that ICER will continue to engage and consider the perspective of patients, caregivers, and other stakeholders to ensure that their evidence reports have the broadest possible relevancy. Again, thank you for the opportunity to comment on the *Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value Draft Evidence Report.* Please contact Sandie Preiss, Arthritis

Foundation National Vice President of Advocacy and Access, ███████████████████
with questions or for more information.

Sincerely,

Sandie O. Preiss

Sandie Preiss
Vice President, Advocacy and Access
Arthritis Foundation

Bendcare
February 17, 2017

To: Institute For Clinical and Economic Review.
Subject: Response to Draft Evidence Report on Targeted Immune Modulators for Rheumatoid
           Arthritis: Effectiveness & Value.

We again applaud this initiative undertaken by the Institute For Clinical and Economic Review.
Systematic review of clinical trials and controlled cohort studies with a view to evaluating the
effectiveness of the growing number of pharmacologic approaches to Rheumatoid Arthritis will provide
valuable insights to those health professionals who serve patients suffering from this debilitating
condition.

We would also like to bring to your attention several opportunities to improve the real-world value of
this, and future Rheumatologic Disease initiatives.

Limiting study data to clinical trials, controlled cohort studies, and carefully selected "grey" literature
constrain conclusions to settings where strict inclusion and exclusion criteria limit applicability to the
larger population that is all patients with Rheumatoid Arthritis. The exhaustive population-wide view of
Rheumatoid Arthritis includes many more sources of important, controllable variability. If the
informatics net were cast more widely, it would be clear that a wide variety of data registries are
available which would permit exploration of these other sources of variability in therapeutic
effectiveness. Examples of existing data registries include physician super groups, provider networks,
clinical specialty labs, national health information systems in countries with country-wide service, and
pharmaceutical manufacturers. Frequently, it is exhaustively knowable who has received a particular
Rheumatoid Arthritis drug, who has been evaluated using a particular specialized lab test, and
therapeutic experiences of many defined populations.

This ICER initiative has been conducted without any detectable investigation of any of the population-
wide sources of information. Those of us that have worked with population-wide information for
decades recognize the symptoms of an informatics process that has been conducted from the
comfortable, carefully circumscribed, narrowly focused traditional approach. Such initiatives are
crippled in their ability to detect attributable risk of serious bad outcomes when comparing therapeutic
alternatives for Rheumatoid Arthritis. However, clinical catastrophes, involving death and or
hospitalization, occur annually on a per 100,000 rate or rarer. They always lack informatics validity per
1,000 population with a particular chronic illness.

To illustrate in a more concrete fashion, let us pose a question. When payors require treatment from one
TNF inhibitor, to another, to another for a patient with unresponsive Rheumatoid Arthritis at high
disease state, is there an attributable mortality rate associated with delayed institution of treatment with a
different mechanism of action? More specifically, how many patient journeys with this therapeutic
trajectory must be observed to detect an attributable mortality rate difference? None of the sources used
in this ICER initiative could detect this difference. However, there are emerging and robust registries
available to support the potential scale of ICER.

Only registries will, for example, have enough Rheumatoid Arthritis patient age 95 or greater to be able
to evaluate effectiveness of various therapies for that age group.

ICER initiatives really should develop processes that make it possible to include population-wide
registry data. The absence of professionals experienced in the use of population-wide data sources on

the committees serving ICER must be addressed before it would be possible to correct this informatics gap.

Finally, the data sources outlined in the Draft Evidence Report will be mathematically inadequate to address the most important issue, which is optimization of management for Rheumatoid Arthritis. Optimization is a curvilinear response, requiring repeated measures designs. None of the cited evidence makes possible assessment of optimization.

We respectfully recommend the inclusion of information from population-wide registries. We would be happy to engage and volunteer times to collaborate and formally participate in your Program Advisory Board. An important next step would be to include in your deliberations professionals with broad experience with such data sources.

Sincerely,

Michael Graven, MD MSc MPH FRSPH
Vice President, Econometrics
Bendcare, LLC

CC:
Andrew S. Ripps
CEO and President
Bendcare, LLC

Bristol Myers Squibb
<center>

Targeted Immune Modulators for Rheumatoid Arthritis: Draft Report

Questions and Comments for ICER
</center>

February 17, 2017

Re: Targeted Immune Modulators for Rheumatoid Arthritis, Draft Report

Bristol-Myers Squibb (BMS) thanks ICER and the New England CEPAC for the opportunity to respond to ICER's request for comment on the draft report, Targeted Immune Modulators for Rheumatoid Arthritis (RA), which was posted January 20, 2017.

Bristol-Myers Squibb (BMS) believes the value in healthcare should be measured by longer, healthier lives of patients. BMS is committed to a comprehensive, evidence-driven approach to value that incorporates patient priorities, real world data, total health system value, multi-stakeholder input and the most up-to-date clinical science. With these key factors in mind, we are providing these comments. We are supportive of value frameworks that are most reflective of the patient experience and support ICER's efforts to incorporate patient groups in the review. Despite the following concerns and suggestions, we are supportive of the inclusion of disutilities for adverse events, which is an integral step in moving towards results that are most reflective of true patient experience and value, and their incorporation of patient groups in the review process.

Below is a list of concerns, clarifying questions and suggestions related to ICER's approach, which we believe will make the final report more informative to the intended audience.

1. It would be helpful to include at the start of the report an executive summary that highlights the key findings of the cost-effectiveness analysis.

2. The use of utility data derived from Health Assessment Questionnaire (HAQ) scores is worrying because the scores are derived from changes in American College of Rheumatology (ACR) scores and modified Total Sharp Score (mTSS), which increases the risk of dilution of effects from over-translation. Increasing the number of steps of translation from one proxy to the next also increases loss of variance in samples, which ultimately is likely to lead to an underestimation of the effects of treatments. This also highlights the need to incorporate real world data into these exercises more generally.

   Recommendation: We suggest that a scenario analysis where the NMA of HAQ results only are used directly to estimate utilities should be undertaken to add context to the final results.

3. Another concern is the use of Wailoo et al, 2008 (1) algorithm for translating HAQ to utilities, and not more-recently developed algorithms from Hernandez et al. 2012, 2013 (2,3). Multiple publications have highlighted that the latter have greater accuracy and have been used in more recent models, including the NICE model (Stevenson et al, 2016). Looking at figure 2 in Hernandez et al 2013 (3) the EQ-5D slope in the naïve linear model is less steep than both observed data and the mixture model, which implies that the conversion algorithm used in the ICER likely underestimates total QALYs gained for all treatments and thus underestimates the incremental ratios.

   Recommendation: We think it would be advisable to incorporate the most recent Hernandez algorithm into the ICER model as the means of translating HAQ

4. An additional concern is how HAQ scores are used to generate estimates of mortality probability. The ICER model focuses on the relationship between levels of HAQ and mortality, but there is evidence

that levels of change in HAQ from baseline decrease the probability of mortality.(4) Exclusion of this factor may underestimate the value of successful treatment in the ICER model.

Recommendation: We think it would be advisable to incorporate Hernandez et al. into the model for the final report.

5. ICER's assumption that patients can only fail after the first six months due to discontinuation may bias the total drug costs in the model because treatment duration is likely to be too long, on average. This assumption for all failed responders likely skews mean costs per patient higher than they would be in the real world. Real-world evidence suggests that many patients are likely to discontinue due to adverse events before six months. In addition, ACR clinical guidelines (see page 4) defines the optimal dosing of RA treatment as that which '…given for at least 3 months before therapy escalation or switching.'(5) As a result, we believe the model's assumption that all patients receive treatment for the first six months may overestimate drug costs for all categories of treatment.

Recommendation: We think ICER should use a mid-cycle correction on cost and benefits for patients who discontinue.

6. By assuming that the short term discontinuation is entirely due to lack of efficacy and not due to AEs, the model biases the results in favor of therapies that have higher rates of AE-related discontinuation. The report states "*the discontinuation assumptions likely overestimate discontinuation in the short-run (lack-of-effectiveness discontinuation), but underestimate discontinuation in the long-run (adverse-event discontinuation)*". In other words, the short-term discontinuation due to AEs is underestimated in therapies that have a higher AE discontinuation like tocilizumab vs. abatacept (4.8% vs. 0.9%; Table 10, pg 60), and on the flip side the overestimation of discontinuation due to lack of efficacy again favors tocilizumab because it has a higher efficacy profile vs. abatacept (ACR < 20 of 38% vs. 42% & ACR >50% of 38% vs. 35%). By using the current assumption, the analysis fails in realizing the efficacy and safety balance of the TIMs. Further, in clinical practice short-term discontinuation is primarily driven by AEs vs. lack of efficacy.(6, 7) It is interesting to note that the frontier analysis on pg 182 show that TIMs with highest AE discontinuation, sarilumab (9.2%) and tocilizumab, dominate other therapies.

Recommendation: In order to reflect clinical practice and also the efficacy/safety balance, we recommend that short-term discontinuation due to AEs be incorporated into the analysis.

7. We also suggest ICER clarify the translation of the unit costs into total lifetime costs, as it currently is opaque. For example, non-drug costs appear to be a direct function of the costs of administration, the costs of monitoring those under treatment and the costs of treating adverse events. Yet, abatacept is shown in the draft evidence report (Table D1) to have the lowest infusion time of any IV drug, and is shown in Table D15 to repeatedly have significantly lower rates of serious adverse events than any other Targeted Immune Modulator (TIM). In addition, according to abatacept's prescribing information the only screening that may be needed is for tuberculosis and viral hepatitis; and, it does not require four yearly blood tests nor liver function tests—abatacept is not metabolized by the liver (8,9). As a result, this does not seem to be appropriately reflected in Table D1. Despite these lower monitoring and adverse event costs, abatacept's non-drugs costs of $93,406-$101,027 lie in the middle of the range of all TIMs ($89,214-107,510).

Recommendation: ICER should produce a clearer explanation of how non-drug costs are calculated for each drug.

8. ICER has failed to acknowledge RA patient heterogeneity by ignoring subgroup analyses, even though ICER acknowledged the complexity and heterogeneity of RA as a disease and the knowledge that the

'fit' for treatment and patient is an important part of clinical management by rheumatologists. Despite "*RA remains a remarkably complex disease to diagnose and manage. There are multiple phenotypic and genotypic variations in the pathogenesis of the disease that affect both the course of RA and the outcome of therapy*" (page 8 para 2).

In particular, the reference to the fact that "*The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed new criteria to facilitate the study of subjects with RA in its earliest stages. The resultant criteria of 2010 (Appendix E) added new predictive biomarkers such as anti-citrullinated* protein *antibody (ACPA) and C-reactive protein. Current recommendations suggest risk stratification based on clinical presentation, biomarker data, and radiographic findings to guide treatment selection.*" (page 8 para 4). Yet no attempt was made to run the cost-effectiveness model for such scenarios to show the variance in value across treatment strategies and the potential value of targeting based on predictive factors for poorer prognosis.

Recommendation: We believe ICER should run scenarios for particular subgroups based on predictive factors for poorer prognosis.

9. Following on from the above point, does ICER plan to make a statement on payers' policies that restrict physician's treatment choice by favoring switching between TNFα inhibitors, before switching to non-TNF biologic agents? Given the emphasis on the potential value of switching between TIMs without restrictions, and in particular between drugs classes such as between TNFα inhibitors and non-TNF biologic agents shown in the pragmatic Rotation or Change (ROC) trial (10) and elsewhere (11-13), the goals and means of maximizing patient value outlined by ICER in this report are unachievable without this freedom.

Recommendation: We believe ICER should explicitly note that payers often require patients to switch between TNFα inhibitors before switching to non-TNF biologic agents.

10. It is not clear in the report that ICER has a preferred order in prescribing conventional DMARD combination treatment, TNFi, or a non-TNFi after failure with conventional DMARD monotherapy. There are conditional recommendations in established RA that discourage TNF-cycling (5), which would also suggest that the algorithm for sequence should be modified, or at least form part of a scenario analysis.

Recommendation: We suggest ICER clarify that there is no preferred order in prescribing conventional DMARD combination treatment.

11. In regards to the Budget Impact, please refer to the letter also attached to this email, *BMS Response to ICER's Call for Improvements to its Value Assessment Framework* that was previously submitted to ICER in September.

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February 14, 2017

RE: Response to Draft Evidence Report on "*Targeted Immune Modulators for RA*"

Eli Lilly and Company is committed to improving outcomes for patients with rheumatoid arthritis (RA), and to advancing the public dialogue regarding drug pricing and value. We appreciate the opportunity to review and provide feedback on ICER's Draft Evidence Report on targeted immune modulators (TIMs) for RA.

RA patient care is unique due to the complexity of the treatment algorithm among distinct patient groups which are defined by disease progression and treatment history. It is important to emphasize that "individual" experience with RA therapy is variable and a "one-size-fits-all" approach does not allow for optimization of individual treatment goals. In Sections 2 and 3 of the report, ICER accurately described the concern with the current access to innovative treatments indicating that "*many payers have created coverage policies which force a particular sequence of treatment [that is not based on clinical evidence but rather on] the largest negotiated discounts and rebates. Specifically, the companies producing adalimumab and etanercept have negotiated first-line use and preferred status in RA limiting the potential for other drugs ...to compete.*" (Section 2.3, page 17). While this is an accurate assessment of real-world challenges associated with access to therapies, ICER's model takes a more desirable approach to medication access that is consistent with recent ACR guidelines (Singh et al, 2016): the model assumes a sequential treatment framework (page 73 of the report) in which each TIM is compared as first-line therapy following failure with a conventional DMARD (cDMARD). The model's assumption of equal drug access should be consistent with the approach used in the model for establishing drug costs. ICER, however, calculated "the net drug price" based on average discounts from wholesale acquisition cost (WAC) for each drug class, which are mainly driven by the current preferred status of a few biologics as well as restricted access for newer therapies (as shown in Table 3 of the report, page 24). Therefore, the net drug price assumption contradicts the model framework. For a new therapy to gain equal access to a preferred drug's access, the rebate discount for the new therapy would need to be significantly higher than the discount for the preferred therapy. We believe this is a fundamental flaw of the evaluation that leads to confusing and inaccurate outcomes. The evaluation should be consistent in its assumptions and should not evaluate equal drug access with an assumption of rebate discounts based on the restricted access.

ICER has correctly identified the current "treat-to-target approach" in RA, which emphasizes the importance of clinical remission as the primary target. However, within this approach current recommendations (Smolen et al, 2016) indicate "while remission should be a clear target, low-disease activity may be an acceptable alternative therapeutic goal, particularly in long-standing disease". This is an important point to consider, especially in patients with comorbidities which might preclude the intensification of therapy to target remission. ICER did not include low disease activity as one of the measures of treatment response. Remission is defined by DAS28 <2.6, SDAI ≤3.3, or CDAI ≤2.8; whereas low disease activity has slightly higher cut off points, i.e., DAS28 ≤3.2, SDAI ≤11, CDAI ≤10. Given the treat-to-target recommendation, we believe the evaluation should include low disease activity, in addition to remission. This would allow for a less restrictive treatment response, especially in patients with established disease usually characterized by significant joint damage and/or presence of comorbidities.

Below are additional concerns about the methodology and specific data points:

1. For the investigational drugs, ICER assumed that "*the annual drug cost equals that of the drug with the same mechanism of action and route of administration (tocilizumab subcutaneous for sarilumab, and tofacitinib for baricitinib)*" (page 74 of the draft report).

   a. It is inaccurate to assume that baricitinib and tofacitinib have "*the same*" mechanism of action. Tofacitinib has a preferential inhibition for JAK1, JAK2, and JAK3, whereas baricitinib has a preferential inhibition of JAK1 and JAK2. This selectivity plays an important role in preferential cytokine signaling and immune cell regulation in the inflammatory cascade seen in RA (Clark et al, 2014). Therefore, ICER should correct the wording from "the same" to "similar" mechanism of action when describing JAK inhibitors.

   b. While the assumption might be an appropriate proxy for the drug cost of the investigational drugs at the time of the report, the assumption may be inaccurate and misleading at the time of these drugs' market launches. ICER should note this assumption in all tables which contain results related to drug costs or their derivatives (e.g., Tables 15-17, Table 20, and all relevant Appendix D tables).

2. Specific baricitinib data inaccuracies and errors:

   a. Baricitinib data from the RA-BEAM trial is described inaccurately on page 44, i.e.:
      i. In the description of baricitinib, the statement about remission rates should say "the clinical remission rates were <u>numerically better</u> among baricitinib patients vs. adalimumab patients and <u>rates of low disease activity achieved were numerically and statistically better</u> among baricitinib patients". The inaccurate statement on the lack of differentiation between baricitinib and adalimumab is repeated again on page 65, in the third paragraph, and should be corrected as well.

      ii.   Radiographic progression data were reported in the Taylor et al (2015) poster presentation and should be included in this section.

      iii.   An additional reference should be added to the HAQ-DI data: Keystone et al (2016).

      iv.   The statement regarding lack of monotherapy data should clarify that there were no monotherapy studies "comparing baricitinib to adalimumab".

b. Section 2.2, last paragraph, makes a statement regarding safety concerns related to an increased risk of herpes zoster ("shingles") infection with JAK inhibitors. Please note that the rate of herpes zoster was similar between baricitinib and adalimumab in the RA-BEAM trial (Winthrop et al, 2016). ICER should clarify its statement and make it more consistent with reported clinical data.

c. Table 6, page 53, and Table C5, page 127, are missing baricitinib data on radiographic progression which was reported for both RA-BUILD (ref. 155 of the report) and RA-BEAM (Taylor et al, 2015) and should be incorporated appropriately.

d. Table C7, page 129, is missing baricitinib data on HAQ-DI from the RA-BEAM trial reported in Keystone et al (2016).

e. ICER did not include baricitinib data on pain, health-related quality of life (EQ-5D, SF-36) and work productivity (WPAI-RA) from available references: Emery et al (2015), Keystone et al (2016), and Smolen et al (2016-1). These data should be incorporated on page 45 and pages 166-169 of Appendix C.

f. Baricitinib data on the rate of serious infections provided in Table D15, page 199, cannot be verified using the reference cited in the table (Dougados et al., 2016). ICER should use Smolen et al (2016-2) for this information instead.

g. Table D16, page 199, inaccurately assumes the same rate of tuberculosis infections among baricitinib and tofacitinib patients. All appropriate baricitinib trials (ref. 84, 138, 155 of this report) have reported occurrence of tuberculosis infections and should be captured appropriately in this report.

3. The assumption of different discount/rebate rates ranging from 5% to 30% across drugs, gives the market leaders a credit for rebating practices which limit other drugs' access and results in patient and physician barriers to innovative therapies. These contracts generally: 1) are contingent upon step therapy (i.e., requiring a trial of 1 or 2 preferred drug(s) prior to using other treatment options); 2) indicate a specific maximum number of drugs that can be preferred for RA (i.e. only 1, 2, or 3 drugs allowed on the preferred drug list); 3) are negotiated across all inflammatory conditions for products with multiple indications rather than by indication; and 4) may include bundling of multiple products with indications outside of RA. Newer drugs may offer higher rebates, a lower net cost to payers, and better clinical outcomes, yet be unsuccessful at securing contracts due to lower existing patient volume across indications, upon which the rebate amount is dependent. <u>This assumption contradicts the model</u>

framework which assumes equal access for all TIMs after cDMARD failure and causes a fundamental flaw in the evaluation. Perhaps, most importantly, this may restrict physicians from selecting the optimal treatment for an individual patient. Instead, ICER should consider the use of WAC with a uniform rebate discount across all drugs which is consistent with the equal access assumption.
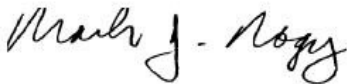
4. Multiple concerns, previously communicated, about the Network Meta-Analysis (NMA) remain. The ISPOR guidelines (Hoaglin et al, 2011) call for "combining studies only if they are clinically and methodologically similar". Use of a random effects model does not "correct" heterogeneity issues, nor does it make patients similar in their disease state and/or treatment continuum. A random effects model does not adjust for study-level differences, but rather for variation in effect size. Therefore, the NMA should be done among patient cohorts from a similar clinical study design to allow for accurate interpretation of results:

    a. A robust justification for inclusion/exclusion of clinical trials within the NMA should be provided, ensuring similarity and homogeneity requirements for a NMA are met.

    b. Clinical trials of cDMARD-IR patients, which include substantial exposure (more than 20%) to biologic DMARDs prior to the trial, should not be included. Inclusion of these trials is methodologically incorrect, as each network in the NMA should only have treatments that are true and feasible options and not allow for inclusion of a treatment where patients have already failed.

5. ICER should provide greater transparency for the NMA, specifically:

    a. An assessment of model fit should be performed and reported.

    b. Heterogeneity assessment should be performed and reported (e.g, the inconsistency parameter (I^2) [Higgins & Green, 2011]; the between-studies variance (tau^2); the heterogeneity statistic Q [Higgins & Thompson, 2002]; Galbraith plots). In case of substantial heterogeneity, a sensitivity analysis excluding studies causing heterogeneity should be performed (ISPOR guidelines).

6. ICER accurately assumes in-class cycling. However, the assumption of reduced efficacy for subsequent treatment (page 73) should apply only to drugs in the TNFi class and not universally. Adjusting the efficacy of secondary/tertiary DMARD, following an insufficient response to the primary treatment across all DMARDs, is not clinically supported or evident from the literature. Carlson et al (2015), provided an assumption of a reduced response rate of 0.84, but applied this assumption only to TNFi agents. This adjustment may be explained by immunogenicity to drugs with the same mechanism of action. We ask ICER to correct this assumption.

7. ICER made the following assumption about discontinuation, page 68: "*Patients discontinued treatment beyond the first six months only due to the occurrence of adverse events*". Therefore, the ICER model considers the rate of adverse events (AEs) as a proxy for long-term treatment

discontinuation and assumes a constant rate of discontinuation. The ICER approach results in a very low discontinuation rate leading to unrealistically long treatment duration with inflated costs and QALYs. Instead, for accurate model evaluation, the discontinuation probability should be a function of treatment response and time on treatment (Cannon et al., 2014) in addition to the rate of AEs. We ask ICER to correct this assumption.

8. Section 4.2 indicates exclusion of dose-ranging Phase II studies; however, ICER has included these types of studies in the evaluation (Fleischmann et al, 2012). Clear rationale should be provided for exceptions from the selection criteria.

9. Table 14, page 75, reports unit WAC as of January, 2017; however, the WAC did not account for the price increase that occurred in January for multiple drugs. ICER should refresh the data on unit WAC and provide a specific date on which the data was pulled.

10. ICER reports payer costs in Tables 15 and 16; however, no definition of this outcome was provided. ICER should describe this variable by explaining what was included in the calculation and how it is different from drug costs.

11. Table 2, page 16, reports patients' out-of-pocket expenses by drug; however, it is unclear how these data were incorporated into the model. Was the payer cost adjusted for the out-of-pocket costs and why? ICER should provide an answer to this question in the report.

We appreciate the opportunity to provide feedback on the draft evidence report, and very much look forward to our recommendations being seriously considered and incorporated into the final model.

Sincerely,

Mark J. Nagy
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Genentech

Genentech
A Member of the Roche Group

February 17, 2017

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Dear ICER Review Panel:

Thank you for the opportunity to provide comments on the ICER draft report titled "Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value." This letter is in response to your request for comments relevant to Actemra® (tocilizumab) and Rituxan® (rituximab). To enhance the robustness of the final report, Genentech recommends ICER address the following:

- **Re-assess the adverse event rate across all Targeted Immune Modulators (TIMs) to ensure consistent literature sources and timeframes are used. Provide transparency on the key clinical trials used to calculate adverse event rates. (Table 10, pg. 60)**
    - When available, use pooled analyses based on clinical trials to describe adverse events and serious infection rates for the TIMs. For example, we are aware of published pooled analyses that report serious infection rates, which differ than the rates in the ICER report.[1,2]

- **Upgrade Actemra's rating from a B+ to an A in monotherapy based on the head-to- head trial ADACTA, as well as extensive clinical data and post-marketing safety experience. (Table 12, pg. 64)**
    - Actemra meets the criteria for an A rating defined in the ICER report as a *"substantial (moderate-large) net health benefit."*
    - Relevant to the other TIMs that received the same rating, Actemra is FDA-approved with long-term clinical and safety experience as well as additional monotherapy data.[3-13]

- **Include additional supportive studies comparing combination therapy such as TIM + conventional Disease Modifying Anti-Rheumatic Drug (cDMARD) to monotherapy with the same TIM or monotherapy to cDMARD (4.2 Results, pg. 30).**
    - Including these studies via an indirect treatment comparison provides a more robust data set, which impacts outcomes and evidence ratings.
    - Specifically for Actemra monotherapy, include the following studies:[10-13]
        - TIM-naïve: Monotherapy vs. Monotherapy + cDMARD (SURPRISE and ACT-RAY)
        - TIM-experienced Monotherapy vs. Monotherapy +cDMARD (ACT-STAR)
        - TIM naïve or experienced: Monotherapy vs. cDMARD (AMBITION)

- **Include language that separates Actemra from the generalized statement:** *"and findings were limited and mixed for TIM monotherapy."* **(4.3 Results pg. 37)**
    - Actemra monotherapy demonstrated consistent efficacy as stated in the report summary conclusion: *"We also identified five studies of monotherapy, two of tocilizumab and three of etanercept; both trials of tocilizumab and two of the three etanercept trials demonstrated substantial and statistically-significantly greater percentages of patients achieving ACR response across all thresholds."*
    - Include three additional Actemra monotherapy studies for completeness.[10,12,13]

- **Correct the statement** *"tocilizumab did not differ from adalimumab in HAQ-DI improvement and other patient reported outcomes"* **to reflect Actemra's improvements in HAQ-DI and other PROs relative to adalimumab. (4.3 Results pg. 41)**
    - Actemra demonstrated statistical significance in the mental component summary (MCS) score of the SF-36 at 24 weeks compared with adalimumab (7.9 vs. 5.0, respectively; p=0.0497).[3,14]

- o Although summary physical component summary (PCS) did not differ between Actemra monotherapy and adalimumab monotherapy, the individual domains of role-physical and vitality demonstrated statistically significant improvement over adalimumab.[3,14]
- o For HAQ-DI, a higher proportion of patients achieved minimum clinically important difference (MCID) on Actemra than on adalimumab (71.3 vs. 64.8, respectively), although this did not reach statistical significance. [3,14]

- **Defer the cost-effectiveness and budget impact modeling of investigational drugs until these drugs are FDA-approved and the price is available. (Table 15, pg. 79)**
  - o Including a speculative price of an investigational drug based on an arbitrary formula into a cost-effectiveness analysis or budget impact model is inappropriate and may be expected to result in misleading conclusions.

- **Provide clarity on the data source and methodology for the sales and utilization data used in the calculation of drug prices used in the draft report. (Table 14, pg. 75)**
  - o Because ICER is using a third-party to obtain drug price, it is unclear how prices were derived and what they represent. We caution that the calculated drug price should not be stated as a definitive fact and that limitations to the analysis should be disclosed.

Please refer to the full prescribing information for complete product indication and safety information, available at:
https://www.gene.com/download/pdf/actemra_prescribing.pdf

https://www.gene.com/download/pdf/rituxan_prescribing.pdf
We welcome the opportunity to provide clarification should ICER have questions on any of these points. Please contact ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

Respectfully Submitted,

Jan Hansen, Ph.D.
Vice President, Evidence for Access
U.S. Medical Affairs, Genentech

Other recommendations and corrections:

	Section	
Page	**Excerpt from ICER draft report**	**Genentech Recommendation**
53	**ACR20/50/70 outcomes across head-to-head trials (Table 5)**	ADACTA[3]: Correct the N and p-values: • N = 163 in TCZ and N=162 in ADA • p-value for ACR20: 0.0038 with ** • p-value for ACR50; 0.0002 with *** • p-value for ACR70: 0.0023 with **
54	**HAQ-DI outcomes across head to head trial (Table 7)**	ADACTA[3]: Correct the N: • N = 163 in TCZ and N=162 in ADA
174-176	**Administration utilization (Table D1)**	Provide references for dose and frequency of administration. Ensure assumptions and sources are consistent across all TIMs. Clinical trial dosing patterns differ from real-world dosing patterns; we recommend using the latter.

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1. Burmester GR, Landewé R, Genovese MC, et al. Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2017 Feb;76(2):414-417.

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3. Gabay C, Emery P, van Vollenhoven R, et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381:1541-1550.

4. Genovese MC, Rubbert-Roth A, Smolen JS, et a. Long-term safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. J Rheumatol. 2013 Jun;40(6):768-80.

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14. Strand CV, Lampl K, Birchwood C, et al. Patient-reported outcomes in two randomized, controlled trials in patients with rheumatoid arthritis treated with tocilizumab monotherapy compared with methotrexate or adalimumab. Presented at: American College of Rheumatology November 11-16, 2016; Washington, DC. Abstract #2515.

Global Healthy Living Foundation
February 17 2017
To: publiccomments@icer-review.org

Thank you for the opportunity to submit comments on the RA draft evidence report. We have many issues with the draft and its methodology. We wish we had more resources to argue these issues so we could better compete with ICER which received its initial $430,000 funding from Blue Shield of California Foundation, and an additional $5.2 million from ex-Enron executive John Arnold's foundation. In addition, our comments may go unnoticed by an ICER board of directors whose majority is connected to the health insurance industry.

Nevertheless, we submit the following response to ICER's RA draft evidence report.

1. When our arthritis community, CreakyJoints (www.creakyjoints.org) began in 1999 our patient events were held in wheelchair-accessible locations with ample space for up to one-third of the participants and their wheelchairs or other assistive devices. Patients were overwhelmingly on cDMARD therapy such as Methotrexate. Biologics, not Methotrexate, took away the wheelchairs. Today, it is rare to see a wheelchair at a community event. What we do see, however, are patients who have cycled through two, three, or more biologics in order to find the one that works for them. Sometimes they switched because of adverse events, sometimes for a lack of success, and sometimes because they were not compliant. All of these factors, and more, need to be considered in ICER's report, not just adverse events. In addition there is one more reason a patient will change a biologic: they are forced to by an insurer because that insurer can sustain a higher profit margin by non-medically switching the patient. Our most common questions from patients are about non-medical switching by their insurance company. Groups like ICER, with its burdensome insurance company bias, can exploit its position in the research community to speed up the non-medical switching trend by creating a seemingly logical structure that allows the false conclusion that the cheapest and oldest drugs are always the best. This is especially true in the RA study.

2. Using short-term clinical trial data ignores the nearly two-decades-old benefits of substituting legs for wheelchairs. Calculating the economic benefits to society derived from sustained worker productivity and quality-of-life that results from the use of biologics is imperative if we claim to exist in a reality-based healthcare paradigm. Just as we would not assess the benefits of a college education by the style of the cap and gown on graduation day, we cannot assess the benefits of rheumatoid arthritis treatments by similar short-term data as used by ICER.

3. We interpret the draft report as being additionally biased toward long-term cDMARD use in that it does not appear to calculate the cost of long-term joint degradation that occurs in some patients. When cDMARDs work, CreakyJoints supports their use unconditionally. When organizations such as ICER, which have an outsized influence on payers, ignore patients for whom cDMARDs don't work to halt joint degradation, we readily accept the benefits of biologics which have been shown to stop joint erosion. ICER should, too. If ICER were recommending cDMARD use with joint erosion vigilance, we would be less troubled by this part of the draft. We have never met a patient who, if given the choice between stopping joint erosion or submitting to future joint replacements chose joint replacements. ICER is choosing joint replacements for them.

4. CreakyJoints, through a multi-year PCORI contract, has built and is populating a patient-reported-outcomes registry of people with arthritis. It is called ArthritisPower. We are using many components of the ICER RA model as instructive of what not to do. This includes reliance on short-term clinical trials data, lack of observational research, dismissing co-morbidities, not clearly defining the benefits of infusion vs. injected, not accepting patient as well as population data, and relying on a small universe of HAQ scores. Instead, we are looking at our growing, long-term patient data which can be combined with clinical and payer data. The objective is to reduce healthcare costs by incorporating societal as well as short- and long-term health benefits with the patient, not the payer, driving the conclusions.

Thank you for the opportunity to submit these comments on the draft report.

Sincerely,

Louis Tharp
Executive Director

Institute for Patient Access

February 16, 2017

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

Re: Feedback on ICER's Rheumatoid Arthritis Draft Evidence Report

Dear Dr. Pearson:

On behalf of the Institute for Patient Access, I thank you for the opportunity to provide feedback on the Institute for Clinical and Economic Review's draft report regarding the cost-effectiveness of alternative Targeted Immune Modulators (TIMs) for rheumatoid arthritis (RA).

About the Institute for Patient Access

The Institute for Patient Access (IfPA) is a physician-led policy research organization dedicated to maintaining the primacy of the physician-patient relationship in the provision of quality healthcare. To further that mission, IfPA produces educational materials and programming designed to promote informed discussion about patient access to approved therapies and appropriate clinical care. IfPA was established in 2012 by the leadership of the Alliance for Patient Access, a national network of more than 800 physician advocates committed to patient access. IfPA is a 501(c)(3) public charity non-profit organization.

Feedback on Draft Report

As ICER's draft report acknowledges, rheumatoid arthritis is the most common autoimmune inflammatory arthritis. It affects approximately 1.5 million Americans. Resulting joint swelling and stiffness can lead to permanent damage, even deformity. Yet TIMs have enhanced patients' ability to cope with the disease on a day-to-day basis, improving functioning as well as duration and quality of life.

IfPA is pleased that ICER's analysis recognizes the value of TIMs as a treatment option for patients with rheumatoid arthritis.

IfPA does have concerns, however, with ICER's conclusion that the price of TIMs exceeds ICER thresholds for cost effectiveness. Health plans may use this conclusion to limit patients' options for RA treatment, despite the fact that ICER's model for calculating cost effectiveness is, arguably, ill-suited for arthritis treatments. IfPA finds ICER's model particularly unfitting for rheumatoid arthritis treatments given the following four points:

1. *ICER's homogeneous cohort does not reflect the reality of treating rheumatoid arthritis' heterogeneous patient population.*

   As ICER notes, "modeling a homogeneous RA patient cohort limits the ability to account for the diverse nature of RA treatment." This limitation is significant.

   Cost-effectiveness estimates based on a homogeneous patient cohort are, in reality, applicable only to the patient population that matches the estimated cohort. Any variability in the actual patient population could create results that deviate from those predicted by ICER's model.

   Thus, cost-effectiveness estimates should, at minimum, come with a caveat specifying to whom the results apply.

2. *ICER's lifetime horizon for calculating cost effectiveness overestimates the duration of patients' treatment with any given therapy.*

   ICER's model simulates the use of therapies over "a lifetime time horizon." Yet one important variability across the RA patient cohort is the length of time patients will use a given treatment. For many patients, the timeframe used in a clinical setting would vary dramatically from ICERs assumptions, significantly altering ICER's cost estimates.

   The average age of a simulated person in the model is 55 years, yielding a lifetime horizon span of 20 to 25 years on average. In reality, TIMs are typically first prescribed for a limited timeframe – six months, for instance. Then, if the patient's arthritis symptoms improve, a doctor will prolong treatment. If patients achieve remission, doctors may slowly phase out the medications.

   Likewise, treatment with traditional DMARDs such as methotrexate are equally unlikely to continue for the time span simulated by ICER's model. Having begun treatment on these therapies, many patients discover that they must progress to a biologic treatment to achieve the response they want. Others find that they cannot tolerate the side effects and must examine additional or alternative treatment options.

   Thus, a substantial gap exists between the time horizon actual RA patients will use a given therapy in a clinical setting and the time horizon that simulated patients use in the ICER model. This gap reduces the reliability of derived estimates. The sensitivity analysis evaluates the "results over short-term horizons," and ICER's simulation partially accounts for some, but not all, of these factors. To yield more realistic results, however, ICER should account for this shorter timeframe in its base model for determining cost-effectiveness.

3. *ICER's budget impact numbers do not accurately reflect rising health care costs in the United States.*

   ICER bases its threshold for "net health care cost growth" on the growth in U.S. GDP + 1 percent. However, overall health care expenditures have been growing faster than this pace; over the past 10 years, for example, the average annual growth in total healthcare expenditures has been 1.5 percentage points faster than the average annual growth in GDP.

By assuming that pharmaceutical spending will grow more slowly than health care expenditures, ICER estimates a cost threshold that is over $140 million smaller and a 13.5 percent lower budgetary threshold.

While a reduction in the growth rate in national health expenditures may be desired, ICER's assumption arbitrarily restricts the growth in the pharmaceutical segment of the health care industry. The cost benchmark should be adjusted to reflect actual growth in U.S. health care expenditures.

4. *ICER's measures of quality do not fully encompass RA patients' experiences.*

While quality-adjusted life year methodology is often controversial, the controversy is heightened with diseases such as rheumatoid arthritis that involve pain and other subjective measures of well-being. QALY cannot adequately reflect all of the factors that impact RA patients and their quality of life.

Moreover, due to the limitations of using a simulation methodology, the ICER model relies upon only the Health Assessment Questionnaire to define quality. This single tool precludes the use of other assessment measures, such as x-rays or other imaging technologies, to diagnose erosive damage to the joints. It therefore presents an incomplete depiction of patients' health quality.

Conclusions

I urge you to consider the input provided here as ICER prepares a final report on rheumatoid arthritis treatments. If IfPA can provide further detail or aid the Institute for Clinical and Economic Review in incorporating any of the above recommendations into its final draft, please contact us at 202-499-4114.

Sincerely,

Brian Kennedy
Executive Director

Janssen

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Thank you for the opportunity to comment on the ICER Report addressing comparative effectiveness and cost effectiveness of TIMs in patients with moderate to severe rheumatoid arthritis (RA). While we have significant concerns about the overall construction and application of this model for decision making in its current state, we are providing critical feedback on clinical and economic issues that must be corrected to address the most significant limitations of the model: 1) Lack of Generalizability; 2) Missing and Incorrect Clinical Inputs for SIMPONI ARIA; 3) Incorrect Dosing Assumptions; 4) Discrepancies in the Annual Cost of Therapy and Need for Use of Average Sales Price for Infused Biologic Agents. In addition, we provide comments regarding more overarching concerns of the General Model Structure and Report Scope.

1) MODEL LACKS GENERALIZABILITY
- The model in its current state offers limited generalizability.
  - The model aims to evaluate the lifetime cost-effectiveness of the first line TIM agent in a sequence of up to 3 TIMs. While the model evaluates biologic naïve patients, it is important to note that the biologic naïve population represents only a small fraction (<15%) of the biologic users covered by US payers (Data on File).
  - We recommend using estimates of discontinuation and treatment duration derived from real-world studies. The model extrapolated the rate of treatment discontinuation due to adverse events derived from relatively short clinical trial periods (24 weeks for most treatments) and applied these to the lifetime horizon in the model. The discontinuation due to AE rates was based on the absolute rates from clinical trials and were not adjusted for various differences across clinical trials. The use of adverse event discontinuation rates for long-term extrapolation have many limitations impacting the validity of the model. Over the long term, patients discontinue treatment for multiple reasons (i.e., loss of efficacy, insurance changes, clinical rationale, and patient preference). There are many published studies on the long-term real world treatment discontinuation rates with TIMs (especially the anti-TNF agents).
- The ICER model uses a common discount across all agents within a TIM class, however net price may differ among payers, therefore conclusions regarding cost-effectiveness may not be generalizable.
- **MODEL/DATA INPUT**
  There are critical errors in the clinical data for SIMPONI SC and SIMPONI ARIA that must be corrected. In addition, inaccuracies were noted in the inputs and assumptions for economic data inputs. The model assumptions and utilities are inconsistent with commonly accepted modeling methods.

2) **SIMPONI SC AND SIMPONI ARIA CLINICAL DATA INPUTS**
- Based upon Table C13, the model inappropriately applies radiographic progression data from SIMPONI SC trials as the model inputs for SIMPONI ARIA radiographic progression. This is a critical flaw in the model because SIMPONI SC and SIMPONI ARIA are entirely different formulations resulting in different pharmacokinetics, efficacy, and safety profiles. As a result, contributions of mTSS to HAQ in Table D6 are underestimated for SIMPONI ARIA.

- **The model should not utilize <u>any</u> data from Kremer et al**. (ICER reference 165) because this trial was not used to support the SIMPONI ARIA indication in RA. This trial utilized the wrong dose of SIMPONI ARIA (q 3-month dosing) which proved not to be effective. This data **must not** be used for consideration in the model.
- The following week 52 data inputs as summarized from Emery et al should be used for SIMPONI SC in Table C13 Sharp Score Data (Emery et al, 2011):

Trial	Intervention 1	Intervention 2	N1	N2	Mean 1	Mean 2	SD 1	SD2
GO-BEFORE	MTX+Placebo	SIMPONI SC 50 mg +MTX	160	159	1.37	0.74	4.56	5.23
GO-FORWARD	MTX+Placebo	SIMPONI SC 50 mg +MTX	133	89	1.1	0.93	4.68	4.86

- The following data inputs based upon GO-FURTHER at week 52 should be used for SIMPONI ARIA in Table C13 Sharp Score Data (Data on File and Weinblatt et al, 2014):

Trial	Intervention 1	Intervention 2	N1	N2	Mean 1	Mean 2	SD 1	SD2
GO-FURTHER	MTX+Placebo	SIMPONI ARIA 2mg/kg + MTX	197	395	1.22	0.13	3.98	3.11

- ACR-scores reported for SIMPONI ARIA in TABLE C3 of the ICER draft report are only partially correct because the model included ACR scores from one invalid source (Kremer et al, 2010 [ICER reference 165]). Further, real world data do not support use of SIMPONI ARIA treatment patterns based upon Kremer et al (Brady et al, 2015). Correct ACR Values for SIMPONI ARIA at 24 weeks are shown below (Weinblatt et al, 2014, Data on File):

Trial	ACR 20		ACR 50		ACR 70		# RCTs
	TIM	DMARD	TIM	DMARD	TIM	DMARD	
GO-FURTHER	62.8%	31.5%	34.9%	13.2%	17.5%	4.1%	1

- HAQ DI improvements at approximately 24 weeks (TABLE C7) are similarly erroneously pooled for SIMPONI SC and SIMPONI ARIA. These should not be pooled but should be listed separately for SIMPONI SC and SIMPONI ARIA. See below for mean improvements in HAQ from baseline for each product, as well as absolute difference in % of patients achieving ≥ predefined MCID threshold at week 24 (Weinblatt et al, 2013; Keystone et al, 2009).

TIMs	HAQ-DI Mean Change from Baseline		% of patients with change ≥ predefined MCID threshold	
	Absolute Difference	Number of Trials	Absolute Difference	Number of Trials
SIMPONI ARIA + MTX	-0.50	1	22.1	1

TIMs	HAQ-DI Mean Change from Baseline		% of patients with change ≥ predefined MCID threshold	
	Absolute Difference	Number of Trials	Absolute Difference	Number of Trials
SIMPONI SC 50 mg +MTX	−0.38	1	29.6	1

ECONOMIC DATA

3) INCORRECT DOSING ASSUMPTIONS:
The model inconsistently and inaccurately applied dose escalation assumptions for various TIMs.
We recommend that the cost-inputs in the model regarding dose-escalation should be consistently applied using real world estimates of dose escalation for products that allow dose escalation in the product labels. On P62 of the ICER draft report, it is stated that "dose intensification may have major cost consequences, particularly to the patient, and dose-tapering strategies have been employed partly to help mitigate these concerns."

- **HUMIRA:** No dose escalation is assumed for Humira (**a key comparator in the cost-effectiveness model**). This is a clear flaw in the model since Humira is the standard upon which all TIMS are compared. The draft report states that 10.5% of patients dose escalate on Humira. Available references have found dose escalation of Humira to occur in 12.6-24.3% of patients (Fisher et al, 2013).

- **REMICADE:** REMICADE provides dosing flexibility for patients with RA. The REMICADE PI recommends that patients be initiated on 3 mg per kg with maintenance dosing every 8 weeks. We recommend a real world practice pattern average dose of 5.5 mg per kg every 8 weeks in RA patients as a more realistic assumption for the model compared to the existing model assumptions. The existing model assumes that more than **40% of patients receive the highest allowed dose of REMICADE (10 mg per kg)** for all administrations. This assumption is inconsistent with known clinical practice or published literature. See Bolge et al for dose escalation assumptions that may be more consistent with clinical practice over the course of a 12-month period (Bolge et al, 2012).

4) DISCREPANCIES IN ANNUAL COST OF THERAPY (TABLE 14) ARE NOTED
- We recommend using ASP as the most accurate net price for TIMs reimbursed under Medicare Part B. **Annual drug cost for REMICADE (average patient weight 77kg)**: We calculate that at a dose of 3 mg per kg and 8 infusions in the first year of therapy using the current ASP of ($822.18 per 100 mg vial), the annual cost of REMICADE would be approximately $15,128 without vial rounding or $19,732 with vial rounding (please note, we believe "rounding" vials is a far less relevant technique and unnecessary and potentially overestimates medication cost when referring to patient populations of appreciable sizes). When dose flexibility is assumed to provide an average dose of 5.5 mg per kg, the cost of the first year of therapy (8 doses) is approximately $27,954. The ICER report estimates annual cost of therapy is approximately $27,556 annually. We agree with the ICER's annual REMICADE cost estimate, assuming average dosing practice of 5.5 mg per kg for induction year (8 infusions). As an additional consideration, the model assumptions are not clear on how REMICADE costs in subsequent years are estimated. It should be noted that **drug costs are expected to be lower after the first year** due to fewer expected maintenance administrations for stable patients (average 6.5 infusions per year).

- **Annual drug cost for SIMPONI ARIA (average patient weight 77kg):** We calculate that SIMPONI ARIA would cost approximately $25,606 as compared to $28,331 estimated by ICER when assuming a dose of 2 mg per kg (3 vials per infusion) and 7 infusions in the first year of therapy using current ASP ($1219.35).
- **Annual drug cost for ACTEMRA (average patient weight 77kg):** Further, the assumptions for annual cost of ACTEMRA therapy reported in Table 14 also appear inconsistent with dosing assumptions in Appendix D Table 1. We estimate that based upon 25% of patients receiving 4 mg per kg and 75% receiving 8 mg per kg at an ASP of $1702.80 per 400 mg, the annual drug cost of Actemra would be approximately $29,700 as compared to ICER estimate of $27,626 annually.

ADDITIONAL CONCERNS
- **COST/QALY**
  Cost/QALY in the ICER report appears inflated compared to that found in the referenced U.S. literature, although we note that few recent studies have attempted to report cost per QALY based upon US currency. These studies may be useful for referencing or comparative purposes. A study comparing Orencia plus methotrexate and Rituxan plus methotrexate to methotrexate alone found that an average of 1.25 and 1.10 additional QALYs were gained per patient, at mean incremental costs of $58,989 and $60,380, respectively (Yuan et al). Likewise, a systematic review by Doan et al found that "Despite differences in design and assumptions, published economic models consistently reported ICERs <50,000 dollars per QALY gained for biologics compared with traditional DMARDs, although ICERs of >100,000 dollars were reported from sensitivity analyses" (Doan et al, 2006; Yuan et al, 2010). As another example, based on the methodology (Carlson et al, 2015) employed by the ICER model, the lifetime incremental cost per QALY calculated for Actemra monotherapy vs Humira monotherapy was $36,944, significantly lower than cost per QALY noted in the ICER model summary.
- **The HAQ microsimulation methodology has numerous limitations** as noted in the published manuscript (Stephens et al). The methodology was designed specifically for use with the population of early, aggressive RA patients in the PREMIER trial. The adaptation of this methodology for the ICER model was not sufficiently detailed to understand the impact of the methodology application on model findings. **We encourage the ICER modeling team to provide explicit detail as to how this methodology was applied (Stephens et al, 2015).**
- There is a lack of transparency regarding assumptions that generate cost in the model.
  - ICER does not disclose exactly how long each patient is on each treatment sequence, the number of doses administered in each sequence (even if on average), whether drug holidays or gaps in therapy were allowed, and how induction dosing was managed. This lack of transparency prevents user validation of cost assumptions.
- **We suggest removing Table 2 since total health care costs, not patient cost-sharing or drug benefit designs, are the focus of the NMA or the CE model.**
  The data in Table 2 could be taken out of context because they suggest that Medicare Part B patients pay more for TIM therapy, when, in fact, they may pay nothing out of pocket. The majority of patients covered under Medicare Part B have some form of supplemental insurance - either through employers, Medicare Advantage plans, or other forms (Cubanksi et al, 2015; Data on File). Supplemental insurance covers the remaining portion of charges not covered by Medicare Part B. In contrast, Medicare Part D patients are responsible for deductibles, co-pays and the Part D donut hole, all of which are not covered by supplemental insurance.

- **Validity of Model Comparators**
  The use of a cDMARD comparator in the model is inappropriate and undervalues the clinical and economic relevance of the model. This cDMARD-only comparator does not reflect the standard of care, nor treatment guidelines in the US. As stated in the ICER draft report (P62), while clinical trials comparing TIMs to cDMARD alone provides important information for incremental benefit, "such a comparison is artificial given that patients have already had inadequate responses to conventional DMARD therapy." The issue is more profound in this model as RA patients managed on TIMS are being compared to RA patients managed on cDMARD for their entire lifetime.

  The assumption that "the HAQ for the cDMARD comparator does not change over time" (P71) is invalid and is contradicted by extensive clinical evidence and significantly biases the model results in favor of cDMARD.
    - A large body of clinical evidence supports that **patient health status deteriorates without effective treatment** (in this case, cDMARD treatment after inadequate response or intolerance to cDMARD) and as a result, HAQ increases over time. **We recommend using the approach of other existing health economic models including two versions of BRAM model from NICE commonly applied a HAQ progression rate of 0.03 to 0.045 per year for patients on cDMARD (Chen et al, 2006).**
    - Further, in patients advancing to palliative care, HAQ scores continue to increase. **We recommend using the commonly applied a HAQ progression rate of 0.06 per year during palliative care used by existing models including the NICE BRAM models. (Chen et al, 2006)**

APPENDICES
- Upon reviewing the appendices, there were over 20 inaccuracies found in the data displayed including either typographical errors or omission of key information.
- In general, critical data for SIMPONI SC and SIMPONI ARIA are missing from the appendices. For example, as previously mentioned, data from the GO-AFTER trial and radiographic data from GO-FURTHER (Smolen et al, 2009; Weinblatt et al, 2014).
- The approved dosing for Janssen products is not consistently accurate. For example, Appendix D, Table D1. See approved Prescribing Information for REMICADE, SIMPONI SC, and SIMPONI ARIA.
- Appendix A defines the strategy for literature review, but a table of complete references should be developed that highlights references included/excluded from the review.
- Appendix C, Table C1 and Figure C19 –DAS28 remission rates at week 24) are available for SIMPONI ARIA from GO-FURTHER (see table below and Bingham et al, 2012). Additionally, FACIT-F scores are available for SIMPONI ARIA from GO-FURTHER). Mean (± SD) improvements in FACIT-F at Week 24 in the SIMPONI ARIA + MTX group were 2.54 ± 10.22 vs 7.96 ± 10.79 in the MTX alone group (P<0.001) (Bingham et al, 2014).

Intervention	DAS28-ESR remission rate	P value
SIMPONI ARIA	17.7%	<0.001

- Inclusion of SWEFOT data are inappropriate for consideration of REMICADE in the NMA or model because the maximum approved dose of REMICADE in Sweden is 3mg/kg, which is not applicable to US usage.

- Appendix C, Table C1: TIMs monotherapy vs conventional: Update the DAS28 ESR remission rate data for SIMPONI SC to reflect the approved dose of 50 mg in combination with MTX. SIMPONI SC is not indicated for use as monotherapy. Data is available from GO-FORWARD in Keystone et al, 2009.
- Appendix C, Table C7 – HAQ data should not be pooled for SIMPONI SC and SIMPONI ARIA, as they are different products with separate clinical trials. SIMPONI SC 100 mg is not an approved dose for RA and it is not indicated for use as monotherapy. Additionally, HAQ data for REMICADE at 6 months are available in ATTRACT (Maini et al, 1999).
- Appendix C, Table C13 –Potential trial design differences are noted for SIMPONI ARIA (GO-FURTHER) and SIMPONI SC (GO-FORWARD).
- Appendix C, Patient-Reported Outcomes – In general, VAS pain scales are reported in most studies of biologics in RA as it is a component of ACR response, yet only 13 references are mentioned here. For example, results for pain assessments are reported in ATTRACT (Maini et al, 1999). Similarly, SF-36 was measured in ATTRACT (Maini et al, 2004).
- Appendix D, Table D1-Information in the "Annual Monitoring Utilization" column does not match that of the Prescribing Information for REMICADE, SIMPONI SC, and SIMPONI ARIA. For example, it is recommended patients be tested for Hepatitis B infection in addition to TB prior to starting therapy (REMICADE, SIMPONI SC, and SIMPONI ARIA Prescribing Information).
- Throughout the ICER report, the ATTEST study is referred to as a "head to head" trial. The definition for "head to head" should be clarified. ATTEST was neither comparative, nor head to head, as stated in Schiff et al "this study was not powered with a superiority or non-inferiority design to compare the two active arms" (Schiff et al, 2008).

VOTING QUESTIONS
- SIMPONI SC, SIMPONI ARIA, and REMICADE have been omitted from consideration by not being included in the voting questions.

References

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Merck

Merck's Response to ICER Draft Evidence Report Titled "Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value" Dated 1/20/2017

To: Steven D. Pearson, M.D., M.Sc. FRCP
President, Institute for Clinical and Economic Review

Dear Dr. Pearson,
Merck values the opportunity to comment on ICER's draft evidence report titled "Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value" (dated: 1/20/2017). Merck's comments on the draft report are as follows:

- On page 16 where it refers to biosimilars in the US, it should include Samsung Bioepis' investigational biosimilar of Remicade (SB2, Infliximab) currently under review by the FDA.
- As multiple biosimilars targeting the disease in question are soon likely to be available in the US market, it is important to include a discussion around implications of biosimilars availability on the price competition and value dynamics in this category.

Comments on the clinical evidence

- In addition to week-30 (Choe J-Y et al., Ann Rheum Dis 2015) and week-54 (Choe J-Y et al., Arthritis Rheumatol 2015) data presented in the draft report, there are week-78 data also available that should be included (citation below, presentation attached). Data pertaining to Figures 3, 4, and 5 in the presentation are provided in the appendix of this letter. These data can be summarized in Tables C2, C4, C18, F1 (pages 229, 256, 297) of the draft report.

  Smolen JS, Choe JY, Prodanovic N, et al. Comparable Safety and Immunogenicity and Sustained Efficacy after Transition to SB2 (An Infliximab Biosimilar) Vs Ongoing Reference Infliximab (Remicade®) in Patients with Rheumatoid Arthritis: Results of Phase III Transition Study [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). (http://acrabstracts.org/abstract/comparable-safety-and-immunogenicity-and-sustained-efficacy-after-transition-to-sb2-an-infliximab-biosimilar-vs-ongoing-reference-infliximab-remicade-in-patients-with-rheumatoid-arthrit/) Accessed February 7, 2017

- 54-week data (Choe J-Y et al., Arthritis Rheumatol 2015) should be included in Tables C2, C4, and C18.
- N's for the 30-week data (Choe J-Y et al., Ann Rheum Dis 2015) should be corrected as follows (pages 125, 127, 130, 283, 297):
    o Infliximab-bio + MTX= 290
    o Infliximab-ref + MTX= 293
- Table C2 on page 125 should include % achieving CDAI remission as follows:
    o Infliximab-bio + MTX= 8.7% (95% CI: 5.2%, 12.2%)
    o Infliximab-ref + MTX= 11.7% (95% CI: 7.8%, 15.6%)
- Table C8 on page 173 should report length of follow-up as 30 weeks (not 54 weeks)
- Table F1 on page 283 should mention that the reported data are for week-30

- Table F1 on page 284 should mention that the reported data are for week-54
- Reference for "Choe 2015" study on Table C2 on page 125 and Table C8 on page 173 should be changed to reference # 178
- Citation for reference # 178 should be updated to the following:

  Choe J-Y, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing sb2, an infliximab biosimilar, to the infliximab reference product (remicade) in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis 2017;76:58–64.

Comments on the economic analyses
- After initially responding to therapy, individuals only discontinue if there is an AE. There is often substantial discontinuation or treatment modification due to progression of symptoms. It is not clear if this waning of protection is considered an AE. The waning of protection needs to be incorporated as it may be important with a lifetime time horizon.
- Costs may be underestimated in the model
  - Medical costs do not appear to include the cost of physical therapy/rehabilitation or home healthcare (e.g., 32% of patients with RA reported requiring physical or occupational therapy when RA was not well-controlled according to the Arthritis Foundation Survey of Rheumatoid Arthritis Patient Treatment Experiences, November 17, 2016, https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf, accessed February 16, 2017).
  - Societal costs do not include the complete burden to the family – it only includes loss of productivity/wages. These do not include other significant costs to the family - e.g. disability, home adjustments, cost of care.[1-2]

Sincerely,
Puneet K. Singhal, PhD
Merck Center for Observational and Real World Evidence (CORE)

References:

1. Ma VY, Chan L, Carruthers KJ. The Incidence, Prevalence, Costs and Impact on Disability of Common Conditions Requiring Rehabilitation in the US: Stroke, Spinal Cord Injury, Traumatic Brain Injury, Multiple Sclerosis, Osteoarthritis, Rheumatoid Arthritis, Limb Loss, and Back Pain. Archives of physical medicine and rehabilitation. 2014;95 (5):986-995.
2. Arthritis Foundation Survey of Rheumatoid Arthritis Patient Treatment Experiences, November 17, 2016. https://www.arthritis.org/Documents/Sections/About-Arthritis/arthritis-facts-stats-figures.pdf, accessed February 16, 2017.

Appendix

Smolen JS, Choe JY, Prodanovic N, et al. Comparable Safety and Immunogenicity and Sustained Efficacy after Transition to SB2 (An Infliximab Biosimilar) Vs Ongoing Reference Infliximab (Remicade®) in Patients with Rheumatoid Arthritis: Results of Phase III Transition Study [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10).

Data for Figure 3

ACR response rate and its 95% CI during the Transition Period Extended Full Analysis Set

	Visit	SB2/SB2		Remicade/SB2		Remicade/Remicade	
		n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
ACR20	Week 54	132/201 (65.7%)	(59.1%, 72.2%)	67/ 94 (71.3%)	(62.1%, 80.4%)	70/101 (69.3%)	(60.3%, 78.3%)
	Week 62	129/193 (66.8%)	(60.2%, 73.5%)	68/ 94 (72.3%)	(63.3%, 81.4%)	67/101 (66.3%)	(57.1%, 75.6%)
	Week 70	118/180 (65.6%)	(58.6%, 72.5%)	61/ 88 (69.3%)	(59.7%, 79.0%)	68/ 98 (69.4%)	(60.3%, 78.5%)
	Week 78	123/180 (68.3%)	(61.5%, 75.1%)	54/ 85 (63.5%)	(53.3%, 73.8%)	64/ 93 (68.8%)	(59.4%, 78.2%)
ACR50	Week 54	87/201 (43.3%)	(36.4%, 50.1%)	39/ 94 (41.5%)	(31.5%, 51.4%)	40/101 (39.6%)	(30.1%, 49.1%)
	Week 62	79/193 (40.9%)	(34.0%, 47.9%)	42/ 94 (44.7%)	(34.6%, 54.7%)	42/101 (41.6%)	(32.0%, 51.2%)
	Week 70	78/180 (43.3%)	(36.1%, 50.6%)	36/ 88 (40.9%)	(30.6%, 51.2%)	43/ 98 (43.9%)	(34.1%, 53.7%)
	Week 78	73/180 (40.6%)	(33.4%, 47.7%)	32/ 85 (37.6%)	(27.3%, 47.9%)	44/ 93 (47.3%)	(37.2%, 57.5%)
ACR70	Week 54	49/201 (24.4%)	(18.4%, 30.3%)	25/ 94 (26.6%)	(17.7%, 35.5%)	23/101 (22.8%)	(14.6%, 31.0%)
	Week 62	41/193 (21.2%)	(15.5%, 27.0%)	22/ 94 (23.4%)	(14.8%, 32.0%)	21/101 (20.8%)	(12.9%, 28.7%)
	Week 70	46/180 (25.6%)	(19.2%, 31.9%)	18/ 88 (20.5%)	(12.0%, 28.9%)	25/ 98 (25.5%)	(16.9%, 34.1%)
	Week 78	46/180 (25.6%)	(19.2%, 31.9%)	19/ 85 (22.4%)	(13.5%, 31.2%)	29/ 93 (31.2%)	(21.8%, 40.6%)

Data for Figure 4

ACR20 Response Rate for Extended Full Analysis Set

Timepoint	SB2/SB2 N=201		Remicade/SB2 N=94		Remicade/Remicade N=101	
	N	n (%)	N	n (%)	N	n (%)
Week 2	201	67 (33.3%)	94	28 (29.8%)	101	28 (27.7%)
Week 6	200	105 (52.5%)	94	47 (50.0%)	101	54 (53.5%)
Week 14	201	123 (61.2%)	94	54 (57.4%)	100	70 (70.0%)
Week 22	201	127 (63.2%)	94	63 (67.0%)	101	72 (71.3%)
Week 30	201	134 (66.7%)	94	65 (69.1%)	101	71 (70.3%)
Week 38	200	126 (63.0%)	94	60 (63.8%)	101	65 (64.4%)
Week 46	201	131 (65.2%)	94	65 (69.1%)	99	67 (67.7%)
Week 54	201	132 (65.7%)	94	67 (71.3%)	101	70 (69.3%)
Week 62	193	129 (66.8%)	94	68 (72.3%)	101	67 (66.3%)
Week 70	180	118 (65.6%)	88	61 (69.3%)	98	68 (69.4%)
Week 78	180	123 (68.3%)	85	54 (63.5%)	93	64 (68.8%)

ACR50 Response Rate for Extended Full Analysis Set

Timepoint	SB2/SB2 N=201		Remicade/SB2 N=94		Remicade/Remicade N=101	
	N	n (%)	N	n (%)	N	n (%)
Week 2	201	16 (8.0%)	94	8 (8.5%)	101	6 (5.9%)
Week 6	200	27 (13.5%)	94	21 (22.3%)	101	16 (15.8%)
Week 14	201	61 (30.3%)	94	30 (31.9%)	100	35 (35.0%)
Week 22	201	80 (39.8%)	94	36 (38.3%)	101	34 (33.7%)
Week 30	201	74 (36.8%)	94	37 (39.4%)	101	43 (42.6%)
Week 38	200	75 (37.5%)	94	39 (41.5%)	101	39 (38.6%)
Week 46	201	80 (39.8%)	94	44 (46.8%)	99	34 (34.3%)
Week 54	201	87 (43.3%)	94	39 (41.5%)	101	40 (39.6%)
Week 62	193	79 (40.9%)	94	42 (44.7%)	101	42 (41.6%)
Week 70	180	78 (43.3%)	88	36 (40.9%)	98	43 (43.9%)
Week 78	180	73 (40.6%)	85	32 (37.6%)	93	44 (47.3%)

ACR70 Response Rate for Extended Full Analysis Set

Timepoint	SB2/SB2 N=201		Remicade/SB2 N=94		Remicade/Remicade N=101	
	N	n (%)	N	n (%)	N	n (%)
Week 2	201	8 (4.0%)	94	0 (0.0%)	101	1 (1.0%)
Week 6	200	12 (6.0%)	94	6 (6.4%)	101	5 (5.0%)
Week 14	201	21 (10.4%)	94	9 (9.6%)	100	15 (15.0%)
Week 22	201	32 (15.9%)	94	14 (14.9%)	101	20 (19.8%)
Week 30	201	39 (19.4%)	94	18 (19.1%)	101	22 (21.8%)
Week 38	200	43 (21.5%)	94	19 (20.2%)	101	20 (19.8%)
Week 46	201	43 (21.4%)	94	23 (24.5%)	99	20 (20.2%)
Week 54	201	49 (24.4%)	94	25 (26.6%)	101	23 (22.8%)
Week 62	193	41 (21.2%)	94	22 (23.4%)	101	21 (20.8%)
Week 70	180	46 (25.6%)	88	18 (20.5%)	98	25 (25.5%)
Week 78	180	46 (25.6%)	85	19 (22.4%)	93	29 (31.2%)

Data for Figure 5

Summary of DAS28 Score by Visit and Treatment Group during Transition-Extension Period Extended Full Analysis Set

| | SB2 | Remicade | | | Total |
| Timepoint | | Overall | SB2 | Remicade | |
Statistics	N=201	N=195	N=94	N=101	N=396
Week 0					
Value					
n	201	195	94	101	396
Mean	6.4370	6.5544	6.5448	6.5634	6.4948
SD	0.78009	0.76309	0.73751	0.78973	0.77303
Week 54					
Value					
n	201	193	94	99	394
Mean	3.9718	3.9816	3.8778	4.0802	3.9766
SD	1.43443	1.36851	1.27443	1.45180	1.40075
Change from Week 0					
n	201	193	94	99	394
Mean	2.4652	2.5765	2.6671	2.4906	2.5197
SD	1.46093	1.45336	1.40802	1.49720	1.45644

| Timepoint | SB2 | Remicade | | | Total |
Statistics	N=201	Overall N=195	SB2 N=94	Remicade N=101	N=396
Week 62					
Value					
n	192	193	94	99	385
Mean	3.9386	3.8943	3.7849	3.9982	3.9164
SD	1.29738	1.41778	1.35326	1.47576	1.35748
Change from Week 0					
n	192	193	94	99	385
Mean	2.4885	2.6638	2.7600	2.5726	2.5764
SD	1.30564	1.54251	1.49928	1.58465	1.43014
Change from Week 54					
n	192	193	94	99	385
Mean	-0.0156	0.0873	0.0929	0.0820	0.0360
SD	0.89526	0.85753	0.91248	0.80653	0.87692

Timepoint Statistics	SB2 N=201	Remicade			Total N=396
		Overall N=195	SB2 N=94	Remicade N=101	
Week 70					
Value					
n	180	184	88	96	364
Mean	3.8636	3.8433	3.8679	3.8208	3.8534
SD	1.41236	1.36132	1.29263	1.42778	1.38491
Change from Week 0					
n	180	184	88	96	364
Mean	2.5502	2.6895	2.6338	2.7406	2.6206
SD	1.49047	1.50183	1.41723	1.58109	1.49578
Change from Week 54					
n	180	184	88	96	364
Mean	0.0471	0.1354	0.0210	0.2403	0.0917
SD	0.87920	0.95614	1.00581	0.90076	0.91870

Timepoint Statistics	SB2 N=201	Remicade			Total N=396
		Overall N=195	SB2 N=94	Remicade N=101	
Week 78					
Value					
n	180	176	85	91	356
Mean	3.8027	3.9787	4.0106	3.9489	3.8897
SD	1.37502	1.43073	1.41735	1.45033	1.40363
Change from Week 0					
n	180	176	85	91	356
Mean	2.6189	2.5546	2.5228	2.5844	2.5871
SD	1.42471	1.53759	1.52472	1.55736	1.47985
Change from Week 54					
n	180	176	85	91	356
Mean	0.1262	0.0048	-0.1226	0.1238	0.0662
SD	0.96284	1.15477	1.35520	0.92147	1.06231

Pfizer

February 23, 2017

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

RE: ICER's draft evidence report on targeted immune modulators for rheumatoid arthritis

Dear Dr. Pearson,

On behalf of Pfizer Inc, I am writing in response to the Institute for Clinical and Economic Review's (ICER) release of the draft evidence report titled "Targeted Immune Modulators (TIMs) for Rheumatoid Arthritis: Effectiveness and Value".[11]

Please note that this letter is being sent at your request in lieu of the original letter we had submitted to you on February 17th. That letter, which was 15 pages long, seems to have violated ICER's existing comment guidelines.

While we appreciate that ICER receives a significant volume of feedback from stakeholders across the spectrum of its workstreams, we are deeply discouraged by this request. The draft evidence report on rheumatoid arthritis (RA) that ICER released was over 500 pages long, and was methodologically dense. Our experts at Pfizer devoted significant hours to the review and assessment of this report, and our response letter reflected not only the depth of this time and effort, but also the extent of the methodological shortcomings we found as a result.

There is a clear inconsistency in the fact that ICER seeks to enforce an arbitrary page limit for stakeholder input, while simultaneously taking the liberty to issue technical materials of unlimited length for review by stakeholders in very short timeframes. As long-time participants in the broader conversation around value in healthcare, we find ICER's request and approach to limiting feedback to be directly counter to the spirit of inclusiveness and seeking partnership-driven solutions that is core to other discussions.

This is the fifth written communication Pfizer is sending to ICER with respect to the Institute's ongoing assessment of advanced rheumatoid arthritis (RA) therapies. Our prior letters have detailed what we believe are significant limitations to the methodology that ICER has used to weigh the clinical and economic value of these important treatments.

After reviewing the draft evidence report released on January 20th, we are acutely disappointed that ICER has not addressed or responded to the concerns we have raised to date. Unfortunately, nearly all of the significant methodological questions we have raised in past communications are still applicable to this version of the report, and we now have additional questions regarding how stakeholder inputs have or have not been used in the development of the draft document.

The ICER website states that the Institute "seeks to play a pivotal role in creating a future in which collaborative efforts to move evidence into action provide a foundation for a more effective, efficient, and just health care system".[12] It is in the spirit of collaboration and with the shared desire to ensure that effective advanced treatments are offered to patients suffering from RA that we are writing to you again today. We are scientists who have spent years studying and advancing the most rigorous methods to understand the clinical and economic value of innovative treatments for RA. We are strongly committed to ensuring that RA patients, their physicians, and all related stakeholders have the best possible evidence base to inform clinical and value based decision-making.

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[11] Institute for Clinical and Economic Review. Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value. Draft Evidence Report. Available at: https://icer-review.org/wp-content/uploads/2016/08/NECEPAC_RA_Draft_Report_012017.pdf. Accessed on January 20, 2017.
[12] Institute for Clinical and Economic Review. About ICER. Available at https://icer-review.org/about/. Accessed on February 9, 2017.

We are disturbed that ICER has continued to take what we view as a fundamentally flawed approach to its assessment of advanced RA therapies, despite the clear and structured advice that we and other leading scientific stakeholders have offered throughout this review process. As it stands, we feel that this report offers no value to RA patients, their physicians, and other healthcare stakeholders who have an interest in improving patient outcomes for RA. In fact, we believe that the draft report has the potential to be detrimental to patients if misguidedly used to limit access to high value therapies.

In the remainder of this letter, we reiterate our top concerns regarding ICER's current approach to examining the value of RA therapies. For each issue we raise, we have sought to detail why we believe ICER's current methodological approach introduces significant error into the assessment. As in the past, we respectfully - but urgently - request that ICER tackle each of our concerns prior to the scheduled release of the next version of the evidence report on March 10th. If these concerns cannot be resolved in that timeframe, we request that ICER hold off on release of the final report and delay subsequent meetings until these critical issues can be fully considered and addressed in an open and transparent manner.

Concern #1: ICER has not addressed or adjusted for significant changes in RA treatments, changes in regulatory guidance for clinical trial design and the impacts these shifts have had on subject enrollment demographics over time.

The first studies examining the efficacy of advanced therapies for the treatment of RA date back over twenty years. Given advances in both science and clinical management of RA, it is important to recognize that newer agents for RA treatment face different thresholds for measures of efficacy than older treatments may have faced. Changes in RA randomized clinical trial (RCT) design over time have been substantively reviewed by Strand and Sokolove[13], and include changes to Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance documents for conducting RCTs in RA.

It is very important that any effort to assess the clinical value of current RA therapies carefully consider and account for differences in clinical landscape and trial design over time. The fact that ICER has not adjusted for these differences means that the results of ICER's assessment are likely biased in favor of older therapies.

Concern #2: ICER's approach to treatment discontinuation and switching does not reflect current standard practice.

The current treatment switching algorithm used in ICER's RA assessment does not reflect treatment guidelines[14] or practice patterns. Current ACR treatment guidelines recommend that if disease activity remains moderate or high following treatment with methotrexate, the standard of care is treatment with a TNF inhibitor or a non-TNF biologic or tofacitinib.[14] If low disease activity is present, then the ACR recommends continuing DMARD therapy, TNF inhibitors, non-TNF biologics or tofacitinib rather than discontinuing respective medication. ICER's treatment algorithm, which limits switching from an initial therapy to another treatment in the same class, does not reflect evidence-based guidelines or clinical practice. Moreover, we remain concerned about the inclusion of two investigational therapies that are not approved by FDA (no indication or dosing recommendation). The value of ICER's assessment is significantly diminished by the lack of alignment with current clinical practice and the inclusion of unapproved therapies.

Concern #3: ICER's approach to ACR classification has not been validated and does not reflect real-world practice.

In its network meta-analysis (NMA), ICER modeled the proportion of patients in four different ACR categories as a key measure of efficacy. This derivation and presentation of ACR scores is highly unusual as it does not align with how such data are traditionally presented in the literature. General practice in the literature is to utilize overlapping categories, such that patients in higher ACR response groups (*e.g.*, ACR70) also are accounted for in lower ACR response groups (*e.g.*, ACR20). ICER's approach creates mutually exclusive categories of response. By utilizing a non-standard method of categorization, ICER confuses readers and potentially encourages an inappropriate interpretation of its efficacy results. ICER's approach to ACR categorization also does not appear to be aligned with existing FDA guidance related to measurement of RA treatment outcomes.**Error! Bookmark not defined.** Has the modeling approach used by ICER been validated in the literature? Is there evidence demonstrating that this approach has clinical relevance? Given that this type of ACR categorization does not reflect the approach taken in current clinical practice, the relevance of this categorization to clinicians and patients seeking to make treatment decisions may be very limited.

[13] Strand V, Sokolove J. Randomized controlled trial design in rheumatoid arthritis: the past decade. Arthritis Research & Therapy 2009; 11(1)1-11.

[14] Singh J, Saag K, Bridges L et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care and Research 2015; 68(1): 1-26.

Concern #4: ICER's approach for analyzing Sharp scores ignores a number of critical methodological challenges and significantly limits both the validity of its findings and relevance to clinical practice.

There are a number of limitations inherent to ICER's current approach to analyzing Sharp scores. First, we believe that ICER has not recognized the statistical challenges inherent to interpreting structural data, given significant data skew. Second, we reiterate our concerns about ICER's use of standard mean difference (SMD) in an attempt to align differences across Sharp score measures. Third, we believe that ICER's decision to reconvert SMD scores back to absolute Sharp van der Heijde figures further complicates and confuses interpretation of results. Fourth, ICER has not addressed whether adjustments were made for the modifications made to both the Genant (1983[15] & 1998[16]) and van der Heijde (1989[17,18] and 1999[19,20]) methods. Fifth, ICER's decision to mix scores from across studies does not account for the fact that Sharp scores are calculated based on the interpretation of clinicians who interpret x-rays. Finally, the issue of time differences raised previously also impacts Sharp score estimation and interpretation.

Concern #5: Estimation of HAQ scores is unnecessary and incongruous, given consistent measurement in clinical trials.

Health Assessment Questionnaire Disability Index (HAQ-DI) scores are measures that are commonly reported in RA clinical trials and may even be more widely used in routine practice compared to ACR scores. ICER acknowledges that the HAQ-DI "was the most widely reported measure of function in most the studies [ICER] identified."[11] Yet in its analysis, ICER elected to estimate HAQ-DI as a function of the calculated ACR and Sharp scores, instead of using the values that were directly measured in clinical trials. We do not understand the rationale for ICER's estimation approach, given the widespread availability of HAQ-DI scores in the clinical literature, as well as the limitations of the ACR and Sharp score data referenced above. This introduces yet another source of potential error into ICER's report.

Concern #6: ICER's estimation of net price discounts is imprecise and should be product-, not class-specific.

We recognize and appreciate ICER's efforts to resolve the challenges around using wholesale prices in its analysis. However, we feel that ICER's approach to calculating discount rates for the various RA therapies included in its analysis is flawed, and leads to inaccurate estimates of cost-effectiveness. We strongly recommend that ICER fully disclose the calculations used to inform the discount data used, to allow appropriate stakeholder input into whether the data and methods are reliable and appropriate for use in the value assessment reports. We further recommend that ICER apply product specific estimates for its net pricing calculations.

Concern #7: There is no evidence that ICER's approach to stakeholder (especially patient stakeholder) engagement has materially informed the report's methodology or findings.

In the draft report, ICER makes several comments that highlight its effort to gather external input on the development of the draft report. For example, ICER notes that (a) clinicians and other stakeholders reported that ACR criteria were difficult to interpret across studies; (b) the ACR criteria are rarely used in current clinical practice given switches to disease activity measures, and (c) physicians are increasingly dependent on long-term registry studies.[11] Yet none of these factors seem to have been taken into consideration in the analysis conducted for the report – in fact, it could be argued that all of those points have been largely ignored, for reasons unclear.

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[15] Genant HK. Methods of assessing radiographic change in rheumatoid arthritis. Am J Med 1983; 75:35–47.

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[17] Van der Heijde D, Van Riel PL, Nuver-Zwart IH, et al. Effects of hydroxychloroquine and sulfasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989; 1(8646): 1036–1038.

[18] Van der Heijde DMFM, Van Leeuven MA, Van Riel PL et al. Biannual radiographic assessments of hands and feet in a three year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992; 35:26–34.

[19] Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999; 26:743–745.

[20] Van der Heijde D, Dankert T, Nieman F, et al. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford) 1999; 38:941–947.

ICER also devotes several pages reporting on the insights gained from two surveys conducted in collaboration with the Arthritis Foundation. We were pleased to see that ICER had engaged this important patient advocacy group, and were interested to see how this work would shape ICER's approach to the RA assessment. We were very disappointed to see that ICER summarized the findings of the surveys, but did not contextualize them in the report. We feel that ICER has missed a critical opportunity to engage one of the largest patient advocacy groups in a meaningful discussion about the methodological approach undertaken in this assessment and how patient preferences could shape the findings of the assessment.

This theme underlies a core challenge with ICER's current approach that has become increasingly evident to us as we have sought to engage ICER in discussions around this RA review: inputs are consistently solicited, but seem to not be adequately considered or meaningfully acted upon. Moreover, it does not seem that ICER offers commenters like Pfizer any direct responses as to why the potential concerns they raised were not considered or acted upon. We ask that ICER leadership reflect on this incongruity between the organization's inclusive ask of stakeholders and its muted response to feedback, not only in terms of the RA report but also with respect to ICER's broader engagements.

Concluding remarks

We respectfully ask again that ICER consider how the limitations identified in this letter may have impacted the findings of the draft assessment. We further ask that ICER make the necessary modifications to its analytical plan to address these issues. If suitable adjustments do not exist or cannot be implemented, we ask that ICER clearly acknowledge how the lack of methodological solutions to the above referenced limitations impacts the value of ICER's findings for the purposes of decision-making.

In closing, we would like to reflect on a statement made in ICER's recent publication titled "Addressing the Myths About ICER and Value Assessment" [21], where you note that ICER holds:

> ...a strong belief that our nation can do a better job of serving the patients of today and those of the future by **looking objectively** at the evidence, **embracing the difficulty** of comparing the value of different treatment options, and **coming together** in a public space to have an honest, civil discourse about the options for how to use evidence as the cornerstone of a more effective and efficient health care system. [emphasis added]

We agree that a collaborative effort to objectively examine clinical and economic evidence to help enable the most efficient use of the healthcare resources in the treatment of RA is a positive goal. We hope that ICER will seek to better recognize and acknowledge the limitations in its draft report and will use this analysis to begin a broader dialogue about how we can utilize current and evolving treatments to best meet the needs of RA patients and their caregivers.

Kind regards,

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[21] Institute for Clinical and Economic Review. Addressing the Myths About ICER and Value Assessment. Available at: https://icer-review.org/myths/. Accessed on February 9, 2017.

<u>**Sanofi Genzyme**</u>

Sanofi Genzyme and Regeneron Pharmaceuticals welcome the opportunity to provide feedback to the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on the comparative clinical effectiveness and value of targeted immune modulators (TIMs) for Rheumatoid Arthritis (RA). Sanofi Genzyme and Regeneron Pharmaceuticals continue to commend ICER for inclusion of the patient voice in the draft report and encourage ICER to be responsive to these patient perspectives by describing how these inputs and preferences are considered and incorporated into the final report. Actively listening, engaging and responding to patients, and incorporating their voice in a meaningful, transparent, and understandable way will ensure integration of value beyond clinical outcomes and cost. Patients are a critical partner in these important decisions.

We also acknowledge ICER's decision to evaluate cost-effectiveness for TIM monotherapy separately from combination therapy with a conventional DMARD (cDMARD). Although we offer support for the methods performed in the comparative clinical effectiveness analysis, we have some important concerns on the cost-effectiveness analysis. Our comments are summarized in the points below and are explained in more detail in the subsequent sections.

- ***Cost-effectiveness.*** The cost-effectiveness analysis should explicitly incorporate HAQ progression for the cDMARD arm given the chronic nature of this disease. Second, we strongly recommend performing sensitivity analyses around the inputs for the utility function. Finally, in the primary cost-effectiveness modeling scenario, ICER allows multiple therapies to differ between the two model arms making comparisons difficult. Although alternative modeling scenarios attempt to test the model's sensitivity to these assumptions, we recommend that ICER account for palliative care in order to fully measure the impact of the treatment sequence.

- ***Specification of comparison treatments.*** As was done for the two JAK inhibitors and the five tumor necrosis factor (TNF) inhibitors, we suggest that ICER limit the description of the mechanisms of the IL-6 class to a broad statement without trying to discern between individual agents.

- ***Comparative clinical effectiveness.*** Evidence for adverse events is limited for investigational agents; however, the report has not utilized all data from the appropriate study that are available for sarilumab. For consistency with other clinical effectiveness analyses, we recommend incorporating data from both investigational doses of sarilumab in the adverse events analysis.

- ***Draft voting questions.*** We suggest that ICER include a voting question regarding the implications of the overall results on cycling and step therapy practices.

These limitations raise concerns about the report's conclusions on the long-term cost-effectiveness of RA biologics and novel oral agents. Below, we outline these issues and provide our recommendations in more detail.

<u>**Cost-Effectiveness**</u>

ICER's models do not take into account HAQ progression in the cDMARD comparison arm. RA is a progressive disease that results in the worsening of disease manifestations over time.[1-3] This worsening of disease activity also extends to previously-treated patients who no longer respond to existing therapies and are therefore in a state that the ICER model refers to as "palliative care". Not modeling any HAQ progression in this state of palliative care, as currently assumed by ICER, implies that patients

remain in their baseline state of disease severity and never worsen, which directly contradicts the available evidence that RA is a progressive disease with worsening manifestations over time.[1-3] Existing health economic models of RA biologic therapies account for the progressive nature of the disease in patients who no longer respond to available therapies by applying an annual progression rate to the HAQ score in states equivalent to that of palliative care.[4,5] For example, the 2016 NICE technology appraisal for RA therapies used a progression rate of 0.045 per year to model patients taking cDMARDs, and a rate of 0.060 per year for patients on palliative care.[6] In fact, a recent comprehensive review of health technology assessments of RA biologic therapies reported that four of the six submissions used 0.045 units per year as their HAQ progression rate.[5] Thus, we recommend that ICER use the most commonly cited estimate of 0.045 for the base-case HAQ progression rate for patients in the palliative care state. ICER should then explore the influence of this parameter in sensitivity analyses using the higher estimate of 0.060.

The cost-effectiveness model does not investigate alternate utilities functions, which would be useful to incorporate as sensitivity analyses. Sanofi Genzyme and Regeneron acknowledge and appreciate that ICER has adjusted the Wailoo et al.[7] equation to better accommodate the model's HAQ scores without requiring an artificial cap at 1. However, we have concerns over the validity of this transformation of the Wailoo equation. Given that ICER has not cited any work validating the new form of the equation, we suggest exploring alternative utility equations to assess the relationship between HAQ and utility in the sensitivity analysis. For example, the NICE health technology assessment of various TNF inhibitor biologics for RA, relied on an equation which defines the utility score as a function of only the intercept and the HAQ score (QoL = 0.862-0.327*HAQ).[4,8] Similarly, Bansback et al. (2005) used a simple linear transformation of the HAQ score and patient sex to estimate the Health Utility Index-III (HUI-3) utility (QoL = 0.76–0.286*HAQ-DI+0.056*FEMALE).[9] Given the range of utility functions in the literature, we strongly recommend that ICER test how sensitive the cost-effectiveness results are to the chosen utility equation through sensitivity analyses.

The report includes additional scenarios for treatment sequence; however, it omits the transition to palliative care in these scenarios. The primary cost-effectiveness results assume patients are treated with an initial TIM, then switch to a second TIM with the same mechanism of action (MoA) as the first, with a third switch to a TIM with a different MoA. This has important consequences for the treatment comparisons specified, in particular for the comparison versus adalimumab. For example, in a comparison between abatacept and adalimumab, first-line treatment of abatacept is assumed to be followed by another non-TNF as second-line therapy, then to a drug with a different MoA (e.g. a TNF inhibitor) as third-line. In the comparator sequence, patients would start on adalimumab, then switch to another TNF as second-line therapy, then to a non-TNF as third-line therapy. Thus, the cost-effectiveness results are a reflection of two different sequences of treatments and not simply a comparison between abatacept and adalimumab.

We appreciate that ICER included additional treatment scenario analyses to address the complexity of RA treatment in practice. Specifically, the second scenario ('Treatment 2 as a Market Basket of all TIMs') provides a cleaner comparison across therapies because only one line of therapy is different between the two model arms. However, the failure to model any additional transitions to palliative care (i.e., cDMARD monotherapy) results in higher incremental cost-effectiveness ratios for all the TIMs. This is why, as ICER notes on page 85, the results of this scenario "seemed to move all ICER findings closer to that of the average TIM versus cDMARD." Since the 'Treatment 2 as a Market Basket of all TIMs' scenario does not model any additional switches beyond the market basket of TIMs, it is not

surprising that higher incremental cost-effectiveness ratios were calculated in comparison to the primary treatment scenario, where non-responding patients transition to the less expensive cDMARD. We recommend that ICER include a transition to palliative care in the alternate treatment scenario 'Treatment 2 as a Market Basket of all TIMs'. This would allow for a more accurate comparison to the primary treatment scenario.

Recommendations:

1. Account for the progressive nature of RA by incorporating HAQ progression for patients in the palliative care state. Specifically, we suggest using a HAQ progression rate equal to 0.045 for the primary modeling scenario.[4-6]

2. Test how sensitive the cost-effectiveness results are to the utility equation through sensitivity analyses with other commonly cited equations.[4,8,9]

3. Include a transition to palliative care in the alternate treatment scenario 'Treatment 2 as a Market Basket of all TIMs'.

Specification of Comparison Treatments

ICER should modify the statement for mechanisms of action for the IL-6 class. On page 12 of the draft report, we ask that ICER modify a statement that attempted to describe the difference in mechanisms between the two IL-6 agents as it is not accurate:

> "IL-6 inhibitors: tocilizumab (Actemra®, Genentech), sarilumab (investigational, Sanofi/Regeneron): The cytokine IL-6 activates T cells, B cells, macrophages, and osteoclasts, and is a pivotal mediator of the hepatic acute phase response to inflammation. Both agents act to reduce IL-6 circulation; tocilizumab binds to the entire IL-6 receptor, while sarilumab targets the alpha subunit of the receptor." (Draft Evidence Report; page 12)

We suggest that ICER use a similar approach to what ICER applied in the description of the two JAK inhibitors and the five TNF inhibitors, and limit the description of the mechanisms to a broad statement without trying to discern between individual agents. An accurate and appropriate wording that we would suggest is from section 12.1 of the USPI for tocilizumab— "Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and has been shown to inhibit IL-6-mediated signaling through these receptors." This is also an accurate statement for sarilumab's MoA.[10,11]

Recommendation:

4. Modify statement about therapeutic mechanisms within the IL-6 class. To be consistent with the format of the TNF and JAK inhibitors descriptions, we suggest the following:

> "IL-6 inhibitors: tocilizumab (Actemra®, Genentech), sarilumab (investigational, Sanofi/Regeneron): The cytokine IL-6 activates T cells, B cells, macrophages, and osteoclasts, and is a pivotal mediator of the hepatic acute phase response to inflammation. These two agents bind to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and have been shown to inhibit IL-6-mediated signaling through these receptors."

Comparative Clinical Effectiveness

The report excludes relevant data from the TARGET study that would appropriately inform the adverse event analysis. In Table 10 on page 60 of the report, data on combination therapy with sarilumab were limited to one of the two investigational arms of the TARGET study (200 mg of

sarilumab + cDMARD; n=184).[12] We would suggest that ICER also include data from the second investigational arm of this study (150 mg of sarilumab + cDMARD; n=181) to generate weighted averages of the events of interest in this table that inform the relevant analyses. Our suggested approach is more consistent with the incorporation of data from both investigational doses of sarilumab in other analyses and commentaries of combination therapy in the report.

Recommendation:

5. Revise adverse events analysis to integrate adverse events from patients exposed to 150 mg of sarilumab in combination with cDMARDs.

Draft Voting Question

We suggest that ICER include a voting question regarding the implications of the overall results on cycling and step therapy practices.
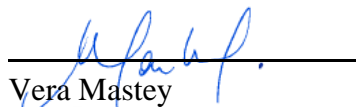
Recommendation:

6. Include the following question: "Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and taking into account other benefits, disadvantages, and contextual considerations, what is the value of routinely initiating patients with adalimumab, with or without cDMARD therapy, as a first line agent before other TIMs?"
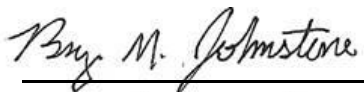
    Low   Intermediate   High

Conclusion

We appreciate ICER's consideration of our comments and recommendations.

Sincerely,

Vera Mastey	Bryan Johnstone
Executive Director Health Economics & Outcomes Research	Regeneron Pharmaceuticals, Inc.
Sanofi Genzyme	

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UCB

UCB, Inc. Comments on ICER Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value Draft Evidence Report

UCB appreciates the opportunity to review and provide feedback on ICER's Draft Evidence Report. UCB is concerned that ICER's draft report underestimates the comparative cost effectiveness of Cimzia®. We also continue to be concerned about ICER's evaluation of the comparative clinical effectiveness of Cimzia which, while favorable, fails to consider key attributes which UCB believes should lead to a more robust comparison.

UCB offers the following comments, which are categorized into four main themes:
1. Overall approach to comparing key pricing/cost inputs;
2. Lack of transparency into key inputs, assumptions, and methodologies;
3. Omissions of key clinical data for Cimzia;
4. Failure to account for other key factors (i.e. dose escalation).

These are significant issues that can result in an inaccurate assessment of the value of Cimzia as it relates to both cost and clinical effectiveness. UCB urges ICER to address these issues in the Final Evidence Report.

1. Overall Approach to Comparing Key Pricing/Cost Inputs

As noted above, UCB is concerned that ICER has underestimated the comparative cost effectiveness of Cimzia. We are concerned that this underestimation results from a fundamental flaw in ICER's overall approach, which compares the WAC prices of products at a single point in time to arrive at a static conclusion of comparative cost effectiveness. While this approach is attractive in its simplicity, it unfortunately ignores the real world complexity of constantly evolving WAC prices and corresponding rebate adjustments in the market. Failure to recognize and account for this dynamic interplay between manufacturers and sophisticated Pharmacy Benefit Managers, health insurers, and public payers will ultimately lead to results that are outdated and inaccurate—not only for Cimzia, but for all products subject to ICER review.

As an example, in ICER's preliminary assessment of RA agents released December 6, 2016, Cimzia compared favorably on both cost and clinical effectiveness. However, in the January 20, 2017 draft report Cimzia compares unfavorably on cost. UCB appreciates the email response from ICER on February 14, 2017, which indicated that the primary reason for this shift was the increase to the WAC price for Cimzia which occurred on January 1, 2017. While this update to the WAC price is accurate, UCB notes that since the release of the January report, at least five of the other comparators have also increased their WAC prices[22]. We assume that ICER will reflect these WAC price increases in the next iteration of its report; however, we note that this version will almost immediately become inaccurate and misleading as well.

This highlights a fundamental flaw in ICER's overall approach, which assesses products at a single point in time, potentially resulting in widely different conclusions depending on something as arbitrary as the

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[22] ProspectoRx by Elsevier/ Gold Standard - February 16, 2017.

timing of the final report. We encourage ICER to consider methods to recognize, update, or otherwise qualify its assessments of comparative cost effectiveness to take this reality into account.

> 2.   *Lack of Transparency into Key Inputs, Assumptions, and Methodologies*

In addition, UCB continues to be concerned about the lack of visibility into the actual inputs, assumptions and methodologies relied upon by ICER, which makes it very difficult if not impossible for stakeholders to reconstruct ICER's calculations. This is a particular concern because of several inconsistencies and/or missing points of clarification in the draft report which could be further distorting ICER's conclusions.

For example, on page 14, Table 1, ICER lists the Wholesale Acquisition Cost (WAC) price for a 200mg syringe or 200mg of lyophilized powder for Cimzia as $3,680. This is incorrect and represents a <u>doubling</u> of the WAC price. As UCB has discussed with ICER, the WAC price for a package of Cimzia, which includes two 200mg syringes (equivalent to 28 days of therapy), is $3,680[23]. Therefore, the correct WAC price for one 200mg syringe of Cimzia is half the price of ICER's input, or $1,840. In fact, Cimzia has the lowest WAC price in the anti-TNF class.

UCB appreciates the email response from ICER on February 7, 2017, asserting that the correct WAC price was, in fact, used to assess the comparative cost effectiveness for Cimzia. However, without a more detailed view into the actual inputs, assumptions and methodologies relied upon by ICER to arrive at its conclusions, it is impossible for UCB to confirm that the correct input was used.

In addition, UCB would like to clarify ICER's inputs, assumptions and methodologies used to calculate the annualized cost for Cimzia. On Table 14, page 75, ICER notes the annualized cost for Cimzia as $34,775. While this is accurate for the first year of a regimen of Cimzia, UCB would like to clarify that this is only true for year one. This is because the first year of Cimzia includes an extra loading dose, leading to an annualized cost of $34,775 for 27 doses (after application of ICER's assumed rebate). However, in year two and beyond there is no need for the extra loading dose, and thus the annualized cost for a year of Cimzia in those years should be $33,488 for 26 doses per year. UCB is unsure whether ICER is appropriately taking this difference into consideration in its calculation of the annualized cost of Cimzia over time.

> 3.   *Omissions of Key Clinical Data for Cimzia*

UCB is concerned about ICER's omission of several key studies and data from the Cimzia label in its evaluation of comparative clinical effectiveness. Specifically, as the evidence for Cimzia demonstrates excellent performance on measures of radiographic progression, we are surprised that ICER's assessment of Cimzia on this measure is unfavorable. UCB requests clarification regarding whether and how ICER incorporated the measures of radiographic progression from the RAPID I study[24]. We also request clarification on whether and how ICER controlled for the differences across randomized clinical trials (RCTs) on this measure.

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[23] Based on WAC Pricing from Elsevier / Gold Standard January 6, 2017.

[24] Keystone E, Heijde D, Mason D, Jr. et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 2008;58:3319-3329.

UCB also requests clarification regarding whether and how ICER recognized the monotherapy indication for Cimzia and the RAPID IV study[25] demonstrating the effectiveness of Cimzia as a monotherapy for patients who have already failed a DMARD. On Table 8, page 57, it appears as though Cimzia monotherapy data were not considered at all. This indication, coupled with our study results which demonstrate excellent performance as a monotherapy for patients who have already failed a DMARD, is a key differentiating clinical factor for Cimzia compared with the other RA agents. The efficacy of Cimzia as monotherapy is formally and specifically recognized by the FDA in the approved U.S. label. Failure to consider this will lead to a significant underestimation of the comparative clinical effectiveness of Cimzia.

In addition, it appears that ICER has omitted the ACR 50 and 70 responses from RAPID I[26]. ACR 50 and 70 are higher standards for measuring response and therefore should also be included for all products. Also, data related to use of Cimzia for women who are pregnant or planning to become pregnant is not included. As the FDA approved labeling for Cimzia contains the data regarding the low placental transfer of Cimzia from mother to fetus, we believe this should have been included by ICER.

UCB understands that some of our studies and data may have been excluded by ICER based on the limitations enumerated in the draft report. However, we have several concerns with these limitations, which we feel do not reflect historical clinical practice or allow manufacturers to apply accepted ethical norms.

For example, we question ICER's assumption that only monotherapy studies including combination therapy arms should be considered, especially when the target population is patients who have already failed a DMARD. There are ethical concerns with requiring patients who have already demonstrated failure on a DMARD due to ineffectiveness or intolerance to continue to take one for purposes of a clinical trial. For this reason, UCB's monotherapy study RAPID IV compares active drug to placebo[27].

Moreover, as measuring ACR response after 24 weeks is an accepted historical precedent in biologic clinical trials, UCB questions ICER's decision to only consider studies of at least 26 weeks. UCB is concerned that ICER is excluding valuable and relevant information based on these limitations.

   4. Failure to Account for Other Key Factors

UCB appreciates ICER's narrative discussion of the impact of dose escalation and differences across randomized clinical trials (RCTs) on evaluations of comparative cost and clinical effectiveness. However, we remain concerned that ICER does not appear to have adequately accounted for either of these issues in its actual calculations.

As noted above, UCB is concerned that a failure to control for differences across RCTs over time may be contributing to ICER's unfavorable assessment of the impact of Cimzia on measures of radiographic

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[25] Fleischmann R, Vencovsky J, van Vollenhoven RF et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis.* 2009;68:805-811.

[26] Keystone E, Heijde D, Mason D, Jr. et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum.* 2008;58:3319-3329.

[27] Fleischmann R, Vencovsky J, van Vollenhoven RF et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. *Ann Rheum Dis.* 2009;68:805-811.

progression. In addition, UCB is particularly concerned that ICER's failure to account for and incorporate the incidence of dose escalation for certain therapies has substantially <u>underestimated</u> their costs and <u>overestimated</u> their effectiveness.

UCB has analyzed commercial claims data and discovered high rates of dose escalation in several RA therapies. We would be happy to share our analysis with ICER upon request. The additional cost of such increased dosing must be accounted for in order for ICER to arrive at an accurate comparison of costs. Similarly, the need to increase the dose for some patients should be factored into the comparative clinical effectiveness calculation for those drugs.

At the very least, since ICER explicitly recognizes the real world impact of dose escalation in the narrative portions of the draft report, there should have been some attempt to quantify this impact and a discussion of how taking dose escalation into account would lead to differences in assessments of overall value. Failure to take this minimal step will deprive payers and policymakers of key information that could alter important decisions impacting patient access.

Conclusion

UCB is concerned by the issues that we have identified in ICER's draft report. As noted above, we are very mindful of the fact that ICER's reports may be relied upon by payers and policymakers (not to mention providers and patients) to make decisions that could greatly impact patient access to the most appropriate therapy for their individual treatment needs. For this reason, we believe it is critical that ICER address the above concerns in the final report.

Should ICER wish to discuss any of these concerns, please contact Alison Anway, Director of Health Policy and Reimbursement at ███████████████████████████

Sincerely,

Patricia A. Fritz
Vice President of US Corporate Affairs
UCB, INC.

United Rheumatology

United Rheumatology   2/17/2017
315 Middle Country Road
Smithtown, NY 11787

Dr. Stephen Pearson
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Dear Dr. Pearson:

On behalf of United Rheumatology (UR), we are pleased to respond to the Draft Evidence Report for *Targeted Immune Modulators for Rheumatoid Arthritis (RA): Effectiveness and Value.* UR supports independent rheumatologists in their mission to strengthen the doctor-patient relationship and provide patient-centered, high quality, cost-effective care. We represent a growing network of 313 physician-members across 118 practices in 29 states. As one of many undertakings, United Rheumatology's Medical Policy Committee has developed Clinical Practice Guidelines for multiple rheumatologic conditions, including Rheumatoid Arthritis. These Guidelines are designed to be actionable standards for high quality, cost-effective treatment of patients and represent the collective understanding of experienced practicing rheumatologists throughout the country.

We have appreciated the opportunity to provide feedback throughout ICER's RA review process, and commend ICER for completing a detailed review of the treatment of RA with medications typically identified in clinical practice as biologic disease modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (such as the JAK inhibitors *tofacitinib* and *baricitinib*) now collectively referred to in ICER's Draft Evidence Report as targeted immune modulators (TIMs). The resulting report is an important reference that underscores the complexity of managing RA in clinical practice and comprehensively summarizes the existing literature comparing the clinical efficacy of TIMs, both currently used and those awaiting regulatory approval, for the treatment of patients with moderate to severe RA.

Broadly, there is an important dichotomy between ICER's recognition of TIMs as a revolutionary advance in the treatment of patients with RA (with their ability to achieve low disease activity/remission as demonstrated by marked reductions in likelihood of joint damage, need for joint replacement surgery, disability as well as reduced mortality), and ICER's conclusion that none of the available TIMs are cost-effective. As written, it is unclear how ICER would recommend addressing this apparent value paradox of biologic therapy; this will, perhaps, become more apparent once ICER writes its Executive Summary.

ICER stated in its recent Webinar on proposed updates to the Value Assessment Framework that "the purpose of [its] potential budget impact analysis is not to suggest a budget cap … for particular drugs in the US health care system" but rather to "signal to stakeholders and policy makers that the amount of added health care costs associated with a new service may be difficult for the health system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients." As ICER only cited examples of how newly introduced drugs would be analyzed in the new framework, it is unclear whether ICER will apply this analysis to *existing* medications such as TIMs approved and in use for nearly 2 decades.

While not specifically addressed by ICER, the notion that none of the biologic treatments demonstrated "cost-effectiveness" within ICER's analytic construct might compel stakeholders to question which *alternative* treatments may be used or may potentially demonstrate cost effectiveness. Specifically, treatment with a combination of conventional DMARDs, methotrexate, sulfasalazine and hydroxychloroquine, known as "triple therapy", was not addressed within ICER's model. It is important that stakeholders understand the implications of moving away from the advances offered by TIMs on patients currently dependent on such therapy. While patients may fare well on triple therapy in idealized clinical trials, triple therapy is, in practice, not an acceptable alternative to TIMs use in most patients. Triple therapy requires patients to take 38-66 pills per week to treat a single condition, may be associated with undesirable side effects, and often results in non-adherence to, or outright discontinuation of, the treatment.

ICER's paradoxical findings of TIMs as revolutionary and clinically effective, yet ostensibly not cost-effective – while not addressing the significant arguments against the practical efficacy of alternative treatments – might be reconciled by addressing several key limitations to the cost analysis that ICER performed. At a minimum, these limitations should be clearly understood by stakeholders in order to avoid misinterpretation and misuse of the report's findings. Below, we have outlined several of these limitations.

- Outcomes in Clinical Trial vs Clinical Practice. One of United Rheumatology's overarching recommendations, which has been shared consistently throughout the drafting of this report, is the critical need to consider the distinction between idealized clinical trial results and those generated in the real-world clinical practice settings where patients receive their care. While we recognize that evaluation of clinical trial data is a critical component of assessing the value of any class of medications, the use of trial data has several recognized limitations when used to generalize responses for modeling patient outcomes in the "real-world" of clinical medicine, including recent RA-specific studies. Patients that volunteer, and are accepted into clinical trials, differ from those in clinical practices in a myriad of measures, often including: (1) disease severity (with those included trials more severely affected); and (2) adherence to prescribed medications (with those in trials more adherent). The ICER analysis would benefit greatly by addressing this distinction clearly and forthrightly.

- Patient Risk Stratification. We commend ICER for its recognition of the often overlooked complexities and nuances of managing RA. In particular, the recognition that some patients may have milder disease that never progresses to significant joint damage or functional impairment regardless of treatment, while others experience a highly aggressive course that may require multiple attempts at treatment, is an important distinction. While ICER additionally notes that "current recommendations suggest risk stratification based on clinical presentation, biomarker data, and radiographic findings to guide treatment selection," the report appears *not* to account for the clinical application of risk stratification within its subsequent modeling. As such, patients with few risk factors for aggressive disease (e.g., normal acute phase reactants, negative RF/CCP, low tender/swollen joint counts, low MBDA score, limited or absent synovitis on ultrasound etc.) were treated no differently within the model than those with many of these risk factors. While we understand that modeling these differences poses its own challenges, ignoring them could make the estimated cost of care across a population of patients with RA higher than that which would be provided in clinics. We believe that a critical element of successfully implementing value-based care models, particularly for the treatment of such variant diseases as RA, is to risk stratify and treat patients accordingly. It may be appropriate to avoid early TIM use in patients with less aggressive disease, while it is critical to more aggressively treat patients at higher risk for long-term joint damage. As ICER similarly recognized, it is simply not possible to prescribe a "one size fits all" treatment approach to RA. It is, however, possible to use real-world clinical data to demonstrate the outcome of appropriately prescribed treatments based on patient risk stratification to deliver "the right medication to the right patient at the right time in the right setting of care."

- Value-Based Model Does Not Acknowledge Potential Cost Avoidance Strategies on the Front End. The model assumes that a certain percentage of patients with moderate to severe RA will fail to respond to cDMARDs such as methotrexate, and thus be prescribed TIMs. In our view, the rheumatology community has not yet fully embraced that optimizing the use of methotrexate, including the use of subcutaneous dosing and altering the dose in response to monitoring of drug metabolism and activity, significantly increases the number of patients with low disease activity or remission on methotrexate. This approach, when effective, limits the need to progress to TIMs, reducing costs while ensuring high quality care. Similarly, measuring therapeutic drug levels of hydroxychloroquine has been proven to unveil significant problems with treatment compliance in many patients. Through risk stratification and the optimization c DMARD use, we believe it is possible to advance a value-based treatment model that enhances, rather than sacrifices, patient results. ICER's modeling fails to address these important topics and only further emphasizes this need.

While UR recognizes the key role that clinicians play in ensuring a patient's access to high-value treatment, several other systematic elements and stakeholders strongly impact our ability to provide the highest value care to our patients. Meaningful reform that achieves these goals will require a combined stakeholder approach, including:

- Evolution to Value- and/or Outcome-Based Drug Pricing. The ICER analysis compares numerous TIMs to an arbitrary preset threshold ($150,000/QALY gained) for cost-effectiveness. Through the use of further simple calculations for each drug, the therapy-specific "price" at which that threshold is met could be calculated. From ICER's perspective, this arithmetically-derived "price" represents a value-derived cost target for the medication. A further refinement of this approach would be to directly measure, rather than model, the improvement in relevant outcome measures (e.g., SDAI, CDAI, DAS28), the outcome-based benefit each drug delivers to a given patient or set of patients. When this data is compared to the cost of each drug, the outcome-based value can be derived, a direct measure of the value of the medication to patients, which then defines the cost applied. A perceived limitation of this approach is the difficulty in obtaining robust data with which to calculate this number. The ability to construct a database among practicing rheumatologists should help address precisely this concern, paving the way for outcomes-based costing. With this data, a variety of arrangements can be envisioned and have been used among various stakeholders to distribute the risk associated with the difference between the expected cost and the delivered value among underperforming medications. This approach might have profound effects on costs in a variety of scenarios.

- The Promise of Biosimilars. The recent development and approval of biosimilar DMARDs (bsDMARDs) presents a potential opportunity for reducing the costs of TIMs. In some ways analogous to the introduction of generic versions of branded drugs, it is anticipated that the cost of bsDMARDs will be modestly lower than their biologic originator (boDMARD) counterparts; however, the cost differential compared to the originator drugs has not yet been determined. Responsible pricing of this new class of drugs holds the potential to reduce system-level and patient costs, assuming that the market's complex pricing models and rebate incentives result in economically-efficient results.

- The Emergence of New Medications. The ICER analysis included two medications that are not currently available in the US, *sarilumab* and *baricitinib*. As physicians, we hope that these products will be priced responsibly, using, where appropriate and possible, value- or outcome-based approaches.

- Additional Modifications to the Cost of the Current Pharmaceutical Supply Chain. There are also certain modifications that could be enacted in the near term, even as preparations for more significant changes are made.

  o Reconsideration of Step Edits. We commend ICER for highlighting the choice-of-treatment constraints faced by providers, and most importantly, our patients. Step edits often require that a patient first try and fail at least two TNF inhibitors before moving on to another class of drug therapy. While ICER recognizes that class switching after the patient's failure to respond to the first TNF yields a greater likelihood of significant clinical response, ICER does not apply this understanding to its model, wherein it assumes that if the first drug selected was a TNF inhibitor the second drug selected would also be a TNF inhibitor. We are hopeful that clinical data may be used to resolve these modeling challenges. From a system perspective, the elimination of such step edits and related tiering incentives would increase competition, including that with newer more effective drugs. By more rapidly achieving remission in a higher percentage of patients, this approach would be expected to decrease costs. Implicit in this altered approach is that practicing rheumatologists embrace detailed recording of disease activity metrics so that an

outcomes based model could identify when patients achieved low disease activity/remission.
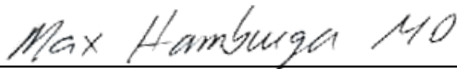
o <u>More Transparency in the Supply Chain for TIMs.</u> The eventual price to patients for TIMs is driven in part by the costs associated with the drug distribution system. A clearer understanding of this system's reliance on discounts and rebates and service fees would help illuminate opportunities to manage the cost of these therapies.

Finally, we have concerns about the Draft Voting Questions that have been proposed for the Public Meeting of the Northeast CEPAC. Specifically:
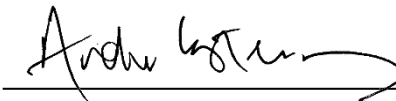
- Eight of the nine questions relate to the comparative effectiveness of 4 specific drugs (*tocilizumab, sarilumab, tofacitinib,* and *baracitinib* -- with and without cDMARDs) in comparison to *adalimumab*. However, two of the considered therapies -- *sarilumab* and *baracitinib* -- have not yet come to market. As a result, four of the nine questions regarding net health benefit will require virtually all of the participants to vote based solely on clinical trial data and cost comparisons presented by ICER, and ***not*** on any prior experience with the drug itself.
- It is unclear why the two currently available TIMs were selected, aside from each having a drug with similar mechanism of action also seeking approval. *Tocilizumab* was the sole bDMARD selected that was felt to be dominant (less costly and more effective than *adalimumab*), yet other dominant TIMs (*rituximab*, *abatacept*, *infliximab*) are not presented to the Roundtable.
- Finally, the ninth proposed question asks about the comparative effectiveness of TIMs "with or without cDMARDs" in comparison to cDMARDs alone. This raises appropriate concerns about triple therapy supplanting TIMs based on its lower cost, yet ICER opted not to critically analyze triple therapy in comparison with TIMs in its Report.

In summary, we congratulate ICER for bringing attention to the ever-rising cost of TIMs, which threatens access to appropriate treatment, and thereby, the health of our patients. However, there are a number of important considerations that should be made to ensure that the ICER analysis adequately addresses the existing and potential cost-saving strategies practiced by clinicians, and the flaws that result when these considerations are ignored in modeling. The ability of practicing rheumatologists to accurately collect and share metrics that measure RA disease activity will hopefully spark interest in a value-based pathway that could lead to further cost savings for this transformative class of drugs.

Sincerely,

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Max Hamburger, MD FACP FACR
President; Medical Policy Committee

_____
                                            Andrew Laster,
MD FACR
Board of Advisors ; Medical Policy Committee

_____
          Andrew Concoff, MD FACR
Medical Policy Committee

Citations available on request

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[iii] Ibid.

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