ABBVIE COMMENTS: ICER RA Draft Report Revised October 11, 2019

DESIGN AND METHODOLOGICAL OBSERVATIONS IDENTIFIED IN REVISED DRAFT REPORT

PATIENT POPULATION:

- ICER's model is limited to a single (homogenous) hypothetical cohort of conventional DMARD inadequate responders (csDMARD-IR), which does not reflect the larger, more complex real-world patient population for which payers provide pharmacy benefits. Only 1 of the 5 phase III upadacitinib trials is included in the economic modeling.
- Notably, the analysis excludes two relevant patient types, i.e. biologic-inadequate responders and mono-therapy patients, which are believed to each make up more than 40% of targeted immunomodulator treated RA patients in practice.¹⁴

CLINICAL ENDPOINTS:

- The model assigns estimated values for HAQ-DI score improvement to generate its measure of effectiveness (QALYs). HAQ-DI is but one endpoint among equally important measures to assess the clinical benefits of treatment. Suppressing disease activity and protection against radiographically detectible joint damage are the other two major, independent and equally important goals for the treatment of RA.^{1-2,32}
- Radiographic progression is excluded from the ICER model. Additionally, clinical trial outcomes important to patients such as pain, fatigue, onset of effect are omitted from the model.

METHODS:

- In keeping with ISPOR recommended best research practices, we recommend the use of empirically generated data rather than estimates that rely on assumptions to calculate data such as EQ-5D results.²⁶⁻²⁹
- The model relies on a series of assumptions to estimate endpoints needed to calculate QALYs. This sequential use of assumed data has not been validated for accuracy and risks the stacking of error and uncertainty to estimate QALYs. (See Fig. 1 below)
- ICER uses <u>DAS-28</u> scores and applies a formula originally derived by Stevenson et.al. to estimate HAQ-DI improvement in biologic treated patients.³¹ Stevenson used <u>EULAR</u> categories to calculate and assign HAQ. However, ICER pools 2 of the DAS-28 categories, and omits DAS-28 *change scores* that are a necessary component to calculate EULAR response. Testing these substantial adaptations is needed demonstrate validity.
- The model uses an outdated method to estimate an older version of the EQ-5D. ICER has acknowledged that the Wailoo model used in the analysis competes with "more advanced" methods of calculating utility in RA. The older EQ-5D instrument is less sensitive, has shown to have a poorer fit, and produces lower estimates for quality adjusted life-years than the EQ-5D-<u>5L</u>.¹⁰⁻¹¹ The EQ-5D-<u>5L</u>, preferably using primary sourced data, is recommended to improve model sensitivity and best fit.
- Using primary sourced EQ-5D-5L data from the SELECT RA trials program while keeping the original four DAS-28 categories intact, Abbvie finds consistently higher utility values for patients with no or low disease activity (NDA or LDA) than were generated by the Wailoo model, along with slightly lower utility values for patients with medium or high disease activity (MHDA).

- The ICER model uses a Markov cohort framework which in recent years has fallen out of favor by health technology assessment organizations because patient-level simulations or hybrid decision tree/patient-level simulations offer advantages over the older method.¹⁵⁻²⁵ Patient-level simulation framework is recommended to attain more accurate results.
- There is a considerable mismatch in treatments for the second line analysis (see table).

Treatment	Clinical	Cost
	data	data
adalimumab	Х	Х
certolizumab		Х
golimumab	Х	Х
infliximab		X
rituximab		Х
tocilizumab		Х
abatacept		Х
etanercept	Х	Х
baricitinib	Х	
tofacitinib	X	
upadacitinib	X	

VALIDATION and SENSITIVITY TESTING:

- Treatment access decisions may be affected by health technology assessments for the complete spectrum of RA patients; which makes it vital to minimize error and validate the assumptions and methods for a decision analytic model.
- In sensitivity testing, we were able to confirm that the model using ICER's assumptions and its choices to estimate EQ-5D produce substantially different results from a model that uses empirically available data from the SELECT RA trials, and the most contemporary methods accepted by other health technology assessors. We also found that other inputs and structural characteristics that led to large variance in the output were cost of 2nd line treatment, and collapsing MDA and HDA categories.

SUMMARY:

- **RINVOQ** is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.³⁰
- RINVOQ's efficacy and safety has been published in clinical trials of cs-DMARD-IR and biologic-IR patients, as monotherapy and combination therapy, and vs Humira+Methotrexate.⁵⁻⁸
- ICER's draft report underestimates the clinical benefits and full value of RINVOQ for the treatment of eligible RA patients due, among other reasons, to the exclusion of key data and patient types and the use of non-validated assumptions of clinical efficacy instead of data generated directly from clinical trials.

SUGGESTIONS FOR CURRENT AND FUTURE RESEARCH:

For over two decades Abbvie has been privileged to work closely with patients and the world's leading rheumatology researchers to develop products that address the unmet needs of this diverse population and deliver value to stakeholders. With that experience in mind, Abbvie

respectfully suggests that future health technology assessments consider the framework outlined below.

Data ascertainment and estimation:

• Consistent with ISPOR best research practice recommendations, data obtained directly from clinical trials or other reliable sources is preferable to the reliance on modeled estimates.²⁶⁻²⁹ Additionally, the fewest number of data transformation steps necessary to arrive at a reliable result is recommended to minimize the potential for error and increase confidence in the final results. When data transformation is necessary, it is suggested that validation and sensitivity testing be conducted first to identify and mitigate potential sources of unintended error.

Spectrum of patient populations:

• Ensures that RA patients, regardless of where they are in their treatment journey or their predisposing factors, are accounted for when assessing value. This may include important subgroups defined by prior treatment history, and conditions of use such as mono-therapy.

Efficacy:

• Measures should utilize endpoints that are clinically meaningful and complete for the purpose of the analysis. Conditions such as RA have multiple outcomes of equal clinical importance. Measures of improvement in signs and symptoms, physical function and inhibition of radiographic progression are each important and describe distinctly different outcomes that cannot be properly assessed in one single measure such as HAQ-DI, EQ-5D, or QALY. Alternative methods to assess value of major endpoints is suggested.

Disease progression:

• Considers short- and long-term treatment improvements and deteriorations in the RA patient journey. The projection of disease activity or HAQ-DI response rates using results at month 3 alone may not provide a complete representation of disease progression or improvement over time. Additionally, radiographic progression over extended periods of time and in the indicated subpopulations is an important factor to assess clinical value.

Safety:

• Incorporates adverse events that are scientifically and medically appropriate for the product(s) assessed.

Costs:

• Captures all healthcare costs, including direct and indirect (societal) costs, over time



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Abbreviations: UPA-Upadacitinib (RINVOQ®), TOFA-Tofacitinib (Xeljanz®, Pfizer Inc), ADA-Adalimumab (HUMIRA®, Abbvie Inc.) BARI-Baricitinib (Olumiant®, Eli Lilly and Co), csDMARDs- Conventional Synthetic DMARDs (e.g. Methotrexate). QALY-Quality Adjusted Life-Year. HAQ-DI – Health Assessment Questionnaire Disability Index. EQ-5D – Quality of Life measure (ICER mathematically estimated).

Amgen Comments on ICER RA Draft Evidence Report (JAK inhibitors)

Amgen appreciates the opportunity to provide comments on the Draft Evidence Report for the *Janus Kinase Inhibitors (JAKs) for Rheumatoid Arthritis (RA): Effectiveness and Value* evaluation. Amgen is a science-based company committed to developing and delivering innovative medicines. Moderate to severe rheumatoid arthritis (RA) is a heterogenous disease that impacts every patient differently, and each patient's response to treatment may be dynamic and vary over time. We believe it is important to consider the existing disease, treatment patterns and economic evaluations so that the current evaluation has the appropriate context. Treatment choice for RA patients should continue to be based on individual patient needs, specific disease characteristics, clinical expertise and patient preference.

Multiple RA reports will be available from ICER with each using different methodologies and comparators. It will be important for the end-users of these reports to understand the various methodologies and impact on results. The new report should be systematic and objective with results descriptions that are transparent, reproducible, credible and rigorous. As the current Draft RA Report is using a new approach with limited comparators and differences in both the model and its assumptions versus the previous 2017 approach, it should be clearly explained so that results can be understood and interpreted appropriately.

The new economic model in this Draft RA report is significantly different from the previous model, which was based predominantly on public models or publications. Additionally, real-world evidence (RWE) has developed over the past few years for several of these drugs, along with an expanded evidence base on the general practice patterns of patient evaluation and therapy changes. While this ICER evaluation focuses on newer products, the physician practice patterns for monitoring and changing therapy is relatively consistent across products. Additionally, RWE and treatment recommendations from available US sources, instead of non-US sources, should form the basis of assumptions for this model. Several aspects of the newly designed model should be addressed to provide a more appropriate comparison between the drugs.

- The evaluation of the disease activity score at 3 months is a key assumption and important factor for drug discontinuation. Clinical trial data evaluating disease activity continuously and as a response endpoint suggests drugs have a further 10% to 50% improvement from week 12 to week 24 (van Vollenhoven et al, 2012; Taylor et al, 2017; Fleischmann et al, 2019). Rheumatology real-world practice data suggests in moderate-to-severe RA patients on a biologic and conventional DMARD combination that disease activity measurements over 12 months occur infrequently and lead to a change in therapy in less than 50% of patients (Yun et al, 20189 Stever 2019). ICER needs to carefully consider the timing of the disease activity evaluation at 3 months, given the RWE variability and implications for early drug discontinuation in patients receiving effective treatment.
- The proposed mapping of DAS to utility is a complex 3-step process with inconsistent assumptions based on intended use of the disease activity measure. In the original ICER RA model (2017), ACR score was mapped to EULAR score. This is a more credible approach of the applied mapping since both these scores incorporate both the change in disease activity and the current state. The proposed mapping of DAS28 to EULAR misses the opportunity to incorporate the dynamic nature of patient change by using a static value. The value of DAS28 is the continuous nature of the score. Clinicians use their clinical evaluation of the patient to determine a need to change therapy. The proposed use of

Amgen Comments on ICER RA Draft Evidence Report (JAK inhibitors)

DAS28 and conversion to EULAR using breakpoints circumvents this judgement by potentially disregarding an effective therapy in improving patients on the cusp of a lower disease activity category. In addition, the mapping to utility from DAS28 to EULAR to HAQ, as stated in the analysis plan likely biases the results due to the differences between DAS 28 and EULAR. We encourage ICER to provide a more precise assessment of disease activity directly to utility, using the continuous data, instead of relying on a multistep process that negates physician judgement.

- In modeling adverse events, ICER is proposing only to include serious infections. The data source for these parameters pre-dates JAKs and thus, does not include JAK data, the drugs of interest (Singh et al, 2011). ICER needs to include additional sources for this safety input to best reflect all drugs in the analysis. JAKs have a set of adverse events that not only include serious infections such as Herpes Zoster, but also vascular events and lipid elevation that could cause significant resource use, patient disutility, and even death over time. Additionally, the approved JAKs have a black box warning in their package inserts pertaining to the above-mentioned adverse events. A model focusing on these drugs that does not include these adverse effects could be considered flawed.
- As RA is a chronic disease, and patients respond differently to products over time, the basecase assessment of the cost-effectiveness should reflect the chronicity of RA and should be longer than 12 months. As the consequences of disease have non-reversible effects on the joints, the impact of these deteriorations should be considered over at least a 10 year, if not a lifetime, time horizon. The 12-month model is additionally limited in the side effects that may occur over time, especially the important cardiovascular effects that have not been included in the model. As a lifetime model is incorporated as a sensitivity analysis, and is a more common assessment time period, ICER should make this more relevant analysis the primary assessment of the model.
- The change in response rate between 1st line therapy and 2nd line therapy is widely accepted to be 10%. The current draft report assumed a difference in response of 16%. The rate difference is quoted from an assessment of Swedish patients, potentially early adopters on TNF is only from 1999-2006. In addition, it appears the publication only provides the rates after the switch, and not in comparison to a first line to second line switch as is the suggested use in the Draft report. We recommend switching back to the 10% change in efficacy for the second-line basket of drugs.

Amgen has been committed to helping patients in Rheumatology for over 25 years and is committed to continuing innovations to support these patients. As a patient-centered organization, Amgen is invested in continuing patient access, and we recognize the importance of robust science that incorporates patient considerations in a fair-balanced manner. We appreciate the opportunity to comment and are look forward to an analysis and model that integrate RWE data reflective of actual RA practice and treatment patterns.

Amgen Comments on ICER RA Draft Evidence Report (JAK inhibitors)

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November 06, 2019

Re: ICER Data Request

Bristol-Myers Squibb (BMS) has reviewed ICER's Draft Evidence Report titled, *Janus Kinase Inhibitor, for Rheumatoid Arthritis: Effectiveness and Value*, in response to ICER's call for Public Comment posted October 11, 2019 on the ICER Website (https://icer-review.org/). BMS has summarized below, by Section, recommendations for your consideration.

Sections 1.2 and 3.1

The draft report recognizes that 2 of the JAK inhibitors, upadacitinib and baricitinib, have black box warnings for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (Section 3.1, page 33). However, please note that all 3 JAK inhibitors, including tofacitinib, have a black box warning for thrombosis, in addition to other safety warnings. Of concern is that these adverse events (AEs) have not been included as part of the Analytic Framework (Section 2.1, Figure 1.1).

- BMS recommends that ICER includes all safety warnings in the model for an accurate and comprehensive safety assessment.

Section 4.1

On page 40, the objective was modified to assess the relative value of JAK inhibitors versus adalimumab for line 1 treatment after failure by a conventional DMARD in moderate to severe rheumatoid arthritis. The report states that adalimumab was chosen as a comparator due to its extensive use in clinical practice for line 1 treatment after failure by a conventional DMARD. Based on this rationale, etanercept could have also been included in line 1 as it is both indicated, and widely used in line 1.¹ Furthermore, although not chosen for this analysis, other agents are used and indicated for line 1 treatment and this is not clearly stated in the report.

- BMS recommends that ICER acknowledge in its report that the model does not fully reflect actual clinical practice and guidelines as they have chosen a simplified and focused update on JAK inhibitors alone. ICER should state that all targeted immune modulators indicated for first line are appropriate treatment choices for providers and patients."

On page 41, the reason ICER provides for treatment switching from line 1 treatment was based on disease activity (specifically as measured by DAS28-CRP, Table 4.1)—with those still experiencing moderately to severely active RA switching to a subsequent line of therapy at the end of the first 3-month cycle. ICER also states that loss of efficacy, adverse events, patient and clinician preferences and access restrictions could be reasons for switching from line 1 treatment to market basket of treatments. However, the latter reasons are not reflected in the model schema on page 44 (Figure 4.1).

- BMS recommends to clarify in the report how switches were assessed since a switching event (or lack thereof) contributes to overall costs and quality-adjusted life years (QALYs). In addition, being that safety is a critical determinant for treatment persistence and may differ



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between TIMs, BMS recommends that ICER consider safety events and discontinuations as reported in the trials.

Section 4.2

A cost-effective analysis (CEA) model structured around the DAS28-CRP endpoint is biased in favor of DMARDs that artificially reduce CRP levels. Because JAK and IL-6 inhibitors interfere with the IL-6 signaling pathway, they affect CRP levels, regardless of changes in RA disease severity, therefore potentially overestimating the efficacy of JAKs and IL-6 inhibitors.²

- BMS recommends to anchor the model on endpoints estimated using DAS28-ESR as opposed to DAS28-CRP because of JAK inhibitors' sensitivity to DAS28-CRP due to their unique mechanism of action.

Which therapies are in the market basket is unclear in the draft report. The model assumptions (Table 4.4, pages 46 to 48), lists only JAKs and TNFis as being in the market basket based on the availability of DSR28 data at 3 months. However, in the economic input assumptions on page 53, abatacept, rituximab and tocilizumab are included. Average net annual prices for all of the therapies are used to determine the net estimated price.

- BMS recommends ICER to clarify which treatments are included in the market basket and to be consistent between cost and efficacy analyses. While BMS understands the use of a market basket for the analyses, therapies included should be the same for both cost and efficacy assumptions.

References:

¹ Symphony Health Systems, PatientSource[®], August 2019 data month, BMS Internal data.

² Smolen JS, Aleta D, Gruben D, Zwillich SH, Krishnaswami S, and Mebus C. Remission rates with tofacitinib treatment in rheumatoid arthritis: a comparison of various remission criteria. *Arthritis Rheumatol.* 2017;69(4):

^{728–734.}



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November 5, 2019

RE: Feedback to ICER's Draft Evidence Report on "Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value"

Eli Lilly and Company appreciates the opportunity to provide feedback to ICER's Draft Evidence Report on "Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value" posted on October 11th, 2019. We would like to offer the following feedback for your consideration:

1. Choice of a comparator and a time horizon in the cost-effectiveness model

a. Both the Scoping Document (released on Jun 28th, 2019) and Modeling Analysis Plan (MAP) (released on August 5th, 2019) indicated ICER's plan to include the following comparisons of Janus Kinase Inhibitor (JAKi) therapies to (1) each other (2) conventional disease modifying anti-rheumatic drugs (cDMARDs) and (3) adalimumab (page 5 of Scoping Document and page 9 of MAP). The Draft Evidence Report has provided comprehensive data on clinical benefits for each JAKi therapy compared to placebo + methotrexate (MTX) for both Targeted Immune Modulators (TIMs)-naïve and TIM-experienced populations at 12 and 24 weeks. The cost-effectiveness analysis objective has been modified to focus on comparison of JAKi therapies to adalimumab only (page 40, first paragraph, Draft Evidence Report). The rationale for this revision was not provided.

This choice of the comparator presents an immediate challenge for the cost-effectiveness analysis due to lack of head-to-head clinical data vs. adalimumab for most JAKi therapies and lack of adalimumab clinical data in the TIM-experienced population. Therefore, we believe this comparator is inappropriate for a cost-effectiveness evaluation, especially in the TIM-experienced population, as the choice is inherently limited. Given most clinical trials in Rheumatoid Arthritis (RA) were conducted versus active comparator arm, i.e., placebo + MTX, ICER should conduct an indirect comparison of JAKi therapies vs. cDMARD as proposed in the MAP. Indirect comparison of JAKi therapies to each other is possible using clinical measures of treatment response (e.g., primary endpoint in clinical trials - ACR) at 12 and 24 weeks of treatment which were reported in the clinical benefit section of the Draft Evidence Report. Possible differences in patient characteristics between clinical trial cohorts should be matched adjusted for the indirect comparison^{1.2}.

b. The choice of time horizon for the base case for the cost-effectiveness model was revised from lifetime proposed in the MAP to one-year horizon in the Draft Evidence Report. The rationale for using such a short period for the base case evaluation is not clear. In the limitations section (page 64) ICER has indicated the following "we chose to model the second line market basket of TIMs over a one-year time horizon, which we believe to be a time period that patients will remain on TIMs irrespective of multiple switches". This assumption is inappropriate for an economic model in RA, which should "include consideration of the connection between the prevention of radiographic progression and downstream economic consequences, and [therefore it is important] to employ lifetime models wherever possible because a long time period is necessary to determine the true cost-effectiveness of agents that modify radiographic progression of RA. In doing so, it is hoped that such [evaluation] will provide optimal information to facilitate important decisions on resource allocation"³. The one-year time horizon leads to misleading results of the model. RA is a chronic progressive disease with expected lifetime use of DMARD treatments. Evaluating one-year incremental cost-effectiveness ratios underestimates the impact of DMARDs use on a healthcare system as was evident from the sensitivity analysis which included lifetime horizon and was

reported in the Appendix Table E10 (page 142 of the Draft Evidence Report). We suggest ICER chooses a longer than one-year time horizon in the base case analysis that is more appropriate for evaluation of a chronic disease such as RA that requires lifetime treatment. The chosen time horizon should be specifically mentioned in the conclusions (page 65 of the Draft Evidence Report). In case of contradictory results from the base case vs. sensitivity analysis, discussion of the impact of the chosen time horizon vs. the lifetime scenario results should be added to the limitations (page 64 of the Draft Evidence Report).

2. Impact of step therapy

We appreciate that ICER have included information in the Draft Evidence Report on the recent publication on impact of plan-level access restrictions on effectiveness and adherence of biologics among patient with RA and Psoriatic Arthritis (PsA) (page 14 of the Draft Evidence Report). Please note the study was conducted in collaboration by Eli Lilly and Company and IBM Watson Health⁴. We would like to point out an inaccurate assessment by ICER of the study findings and limitations. First, the study found that access restrictions were common: one-third of those studied had access restrictions to at least one biologic or targeted synthetic DMARD treatment through step therapy or prior authorization or both. And of those with restrictions, nearly 70% of people with RA and 79% of people with PsA were enrolled in plans that required step therapy with or without prior authorization.

Second, among individuals with RA whose plans require step therapy to their RA treatment, medication adherence was 18% lower and odds of treatment effectiveness were 17% less compared to people with RA who did not have access restrictions. The impact of step therapy among people with PsA was even higher: medication adherence was 27% lower, and the likelihood of treatment effectiveness was 25% lower compared to people with PsA in plans without access restrictions.

Finally, study results show that people in plans with step therapy have additional healthcare resource use throughout the course of an individual's coverage period. For example, individuals with RA whose plans required step therapy were three times more likely to be admitted to the hospital due to an infection, and nearly twice as likely to visit the emergency room during the study compared to people with RA in plans without step therapy restrictions. In addition, those with access restrictions filled prescriptions for glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) more often, which could be an indication of poorly managed disease.

Given the above findings, we do not believe that the reported step therapy effect size is small as ICER has pointed out in the Draft Evidence Report. The study was conducted using patient-level data and had an appropriate sample size to detect statistical differences between the study cohorts (the study included 3,993 people with RA and 1,713 people with PsA). The difference between patients in plans by restriction level should be expected as selection into these plans should not be based on patients' characteristics. These differences should not be over-adjusted by propensity score matching as the purpose of the study was to measure the impact of these differences on treatment outcomes. Among the baseline characteristics, only urban residence, proportion of patients with diagnosis of chronic respiratory condition, diabetes, hypertension, and osteoarthritis showed a statistical difference between the study groups. Regression adjustments conducted in the study were sufficient to account for these differences between cohorts.

3. Clinical data and coverage information reported for baricitinib

a. Baricitinib coverage by UnitedHealthcare – Employer & Individual (UHC - commercial) described on page 16 of the Draft Evidence Report is outdated. As of November 1st, 2019, UHC has prior authorization criteria for baricitinib in alignment with the FDA label⁵, allowing access to RA patients diagnosed with moderately to severely active RA that have a history of failure, contraindication, or intolerance to at least one TNF antagonist therapy.⁶ Also, baricitinib will gain preferred brand tier drug status with UHC- commercial effective January 1st, 2020.⁷ We ask ICER to update the coverage information for baricitinib with UHC.

- b. ICER incorrectly reports a lower significance level for baricitinib ACR20 and ACR70 response rates in Table 3.5, page 32 of the Draft Evidence Report. The report should have '*' next to both ACR20 and ACR70 response rates denoting p<0.001 as reported in Genovese et al. (2016), Table S4 of Supplementary Appendix⁸. We ask ICER to make this correction.
- c. Appendix Tables: D5, D6, D10, and D14, do not report baricitinib data from RA-BUILD and RA-BEACON clinical trials. Below we provide references where these data were reported. Please note that publications on clinical trials usually have Supplemental materials or Appendixes that are provided in a separate file along with the main publication. We ask ICER to include the complete clinical data for baricitinib in the report.

Draft Evidence Report Table	Clinical Measure	Reference
D5	Baseline CDAI	RA-BUILD: Dougados, 2017, Table S2, page 19 of Supplementary data ⁹ RA-BEACON: Genovese, 2016, Table S2, page 15 of Supplementary Appendixes ⁸
D5	Baseline Concomitant cDMARD use	RA-BUILD: Dougados, 2017, Table S2, page 19 of Supplementary data ⁹
D6	Baseline FACIT-F	RA-BUILD: Emery 2017, Table 1, page 4 ¹⁰ RA-BEACON: Smolen, 2016, Table S1, page 2 of Supplementary data ¹¹
D6	Baseline SF-36	RA-BUILD: Emery 2017, Table 1, page 4 ¹⁰ RA-BEACON: Smolen, 2016, Table S1, page 2 of Supplementary data ¹¹
D10	12-week FACIT-F	RA-BEACON: Smolen 2016, Table 1, page 5 ¹¹
D10	12-week SF-36	RA-BEACON: Smolen 2016, Figure 2, page 4 ¹¹
D14	24-week FACIT-F	RA-BEACON: Smolen 2016, Table 1, page 5 ¹¹
D14	24-week SF-36	RA-BEACON: Smolen 2016, Figure 2, page 4 ¹¹

Thank you for the opportunity to provide feedback to ICER's Draft Evidence Report and we hope you will consider our suggestions and revise the Evidence Report accordingly to improve the quality and relevance of the conclusions of the evaluation and the report.

Sincerely,

Mark J. Nogy

Mark J. Nagy Vice President, Global Patient Outcomes and Real World Evidence Eli Lilly and Company 317-276-4921 nagy mark j@lilly.com



November 8, 2019

Institute for Clinical and Economic Review One State Street, Suite 1050 Boston, MA 02109

Dear ICER Review Panel:

Genentech, a member of the Roche Group, is deeply committed to addressing the unmet medical needs of patients with rheumatoid arthritis (RA). RA is a chronic and complex disease, and patients commonly encounter barriers that delay appropriate care.¹⁻³ Early and timely access to therapies targeting different mediators of inflammation is crucial in preserving patients' physical function and reducing disability.

We appreciate the opportunity to provide comments on the Draft Evidence Report published on October 11, 2019, and we commend ICER's efforts to align the report with current clinical practice. To more accurately reflect real-world treatment and inform real-world decision making, we suggest the following recommendations to enhance the utility and clarity of the report:

- 1. Adopt a lifetime time horizon for the base-case analysis to sufficiently capture all costs and outcomes for patients with RA;
- 2. Use the Disease Activity Score 28-joint count (DAS28) calculated using erythrocyte sedimentation rate (ESR) to assess disease activity in the cost-effectiveness model;
- 3. Expand the second line market basket to include the best available evidence from all targeted immune modulators (TIMs);
- 4. Provide disclaimers around the limitations of the model and differences from the previous report to reduce the risk of misinterpretation by decision makers.

1. Adopt a lifetime time horizon for the base-case analysis to sufficiently capture all costs and outcomes for patients with RA.

A one-year time horizon is not appropriate for evaluating the long-term cost-effectiveness of interventions for RA. Best practices for cost-effectiveness modeling recommend adopting a time horizon long enough to capture all health effects and costs.^{4, 5} Although ICER used a one-year time horizon to mitigate the uncertainty surrounding the number of subsequent lines of therapy, this assumption does not reflect real-world treatment patterns, outcomes, and costs. A one-year time horizon fails to account for the chronic nature of RA in which treatment with TIMs can be lifelong even if patients achieve remission.^{1, 2} Therefore, to assess the *long-term* cost-effectiveness of an intervention, a lifetime time horizon should be used to reflect the disease course of RA and treatment with multiple lines of therapy.

If a lifetime time horizon is not adopted for the base-case analysis, at a minimum, the results of a lifetime scenario analysis should be discussed in the "Long-Term Cost-Effectiveness" chapter, the "Executive Summary," and the "Report-at-a-Glance." While an intervention may be considered cost-effective over the short-term (i.e. one year), it may not be cost-effective over the course of a patient's lifetime. Not discussing the results of both time horizons together may provide an incomplete picture to health care decision makers about the *long-term* cost-effectiveness of interventions.

2. Use the DAS28-ESR to assess disease activity in the cost-effectiveness model.

The DAS28-ESR should be used to assess disease activity in the cost-effectiveness model rather than the DAS28 calculated using C reactive protein (CRP). Using the DAS28-CRP rather than the DAS28-ESR may overestimate remission rates for targeted immune modulators that target specific inflammatory cytokines, impacting the validity of the cost-effectiveness model.^{6, 7} While DAS28-CRP and DAS28-ESR may overestimate response compared to other measures, targeted therapies can have a differential impact on CRP levels and ESR. Agents inhibiting interleukin-6 (IL-6) and Janus kinase (JAK) signaling lead to a rapid reduction in CRP levels while not affecting ESR to a similar extent. Although treatment guidelines do not distinguish between the DAS28-ESR and the DAS28-CRP, the threshold values to determine disease activity (e.g. remission, low disease activity) correspond to the DAS28-ESR.^{1, 2, 8} Therefore, applying the DAS28-CRP to the recommended threshold values in this update may overestimate the efficacy of JAK inhibitors, potentially mischaracterizing their value.

3. Expand the second line market basket to include the best available evidence from all TIMs.

ICER should use the best available clinical and economic information from all TIMs to inform the second line market basket, including data submitted as academic-in-confidence during the course of this update. For example, incorporating data from clinical trials of Actemra[®] (tocilizumab) in TIM-experienced populations (e.g. RADIATE, ROSE, SUMMACTA, ACT-STAR), submitted to ICER on July 12, 2019, can better reflect real-world treatment options. By including this data ICER can also better align the TIMs selected to inform the efficacy parameters with those informing the cost parameters of the model.

4. Provide disclaimers around the limitations of the model and differences from the previous report to reduce the risk of misinterpretation by decision makers.

The "Executive Summary" and "Report-at-a-Glance" should highlight the limitations of the costeffectiveness model and explicitly state that the results of the JAK inhibitor update should not be directly compared to the results of the 2017 RA report.⁹ For this update, ICER made substantial changes to the scope of the report and to the structure of the cost-effectiveness model. The extent of changes and the limitations of these changes should be sufficiently documented in various sections of the report and related materials. Adopting this recommendation can facilitate more informed interpretations and discussions by health care decision makers as they evaluate TIMs for the treatment of RA.

Conclusion

RA is a chronic and complex disease requiring a personalized approach to treatment. Patients, providers, and payers require the best available evidence to make informed decisions. We believe our comments will enhance the utility and clarity of the RA report, and we welcome the opportunity to discuss these recommendations further.

Sincerely,

Jan Elias Hanger

Jan Elias Hansen, PhD Vice President, Evidence for Access U.S. Medical Affairs, Genentech, Inc.

1125 Trenton-Harbourton Road Titusville, NJ 08560



Date:

RE: ICER Rheumatoid Arthritis Draft Evidence Report – Response to Request for Public Comment

The following information is provided in response to request for public comment and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information for each product [Remicade, Simponi, Simponi Aria], including the following sections: INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND ADVERSE REACTIONS.

CONTACT INFORMATION		
Name	Shantel Gooden, PharmD	
Organization	Janssen Scientific Affairs, LLC.	
City, State	Horsham, PA	
Email Address	Sgooden2@its.jnj.com	
EXECUTIVE SUMMARY		

Janssen appreciates the opportunity to comment on the ICER Draft Evidence Report for the Assessment of Treatments for Rheumatoid Arthritis. We believe there are opportunities to strengthen the discussion in the areas of coverage policies for infliximab and infliximab-dyyb, interchangeability guidance, and longer-term assessment of rheumatoid arthritis therapies.

- Considering the variation in coverage among regional payers, we recommend that the ICER report focus on the national insurers. However, it should be noted that even focusing on national insurers, all policies are subject to change year to year. The dynamic changes in insurance coverage could invalidate an assessment of coverage comparisons, particularly since coverage continually changes and as new therapeutic options become available.
- The PLANETRA extension study is presented as a possible study for addressing the FDA's requirements on interchangeability designation. However, the PLANETRA extension study does not meet the design elements required for a switching study to support interchangeability designation. To-date, no dedicated interchangeability studies with either infliximab-dyyb or infliximab-abda have been conducted.
- A longer time frame, beyond the one-year horizon used in the base case, would be more appropriate for capturing the long-term benefits of disease modifying drugs and the effect of switching seen over the course of long-term treatment.

SUMMARY OF COVERAGE POLICIES & CLINICAL GUIDELINES

Section 2.1, Pages 16-17, Coverage Comparison of Infliximab and Infliximab-dyyb:

- The report states that UHC designates infliximab as the preferred product compared to infliximab-dyyb.
- However, this does not reflect changes to UHC coverage made in 2019.
 - Effective October 1, 2019, infliximab (Remicade) and infliximab-dyyb (Inflectra) are co-preferred for UnitedHealthcare commercial plans.¹
 - Effective June 1, 2019, UnitedHealthcare Community Plan requires use of infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis) prior to use of infliximab (Remicade).²
- The report also describes coverage decisions from select regional payers (i.e., Kaiser Permanente, Health Net, and Medi-Cal). However, there is variation among regional payers, with many regional payers offering both Remicade and biosimilars, and some that prefer the biosimilar over Remicade. Also, within a payer, there are coverage changes year to year with different products getting preferred or equal status.
- Considering the variation in coverage among regional payers, we recommend that the ICER report focus on the national insurers based on the greater number of covered lives represented.

• Changes in coverage broadly reflect the competitive dynamics in both national and regional insurers and could invalidate an assessment of coverage comparisons, particularly since coverage continually changes and as new therapeutic options become available.

COMPARATIVE CLINICAL EFFECTIVENESS

Section 3.4, Pages 37-39, Biosimilars for RA, subsection "Infliximab Biosimilar (Inflectra/CT-P13/Infliximab-dyyb):

- In this section, the PLANETRA extension is presented as a possible study for addressing the FDA's requirements on interchangeability designation. However, the PLANETRA extension study does not meet the design elements required for interchangeability designation.
 - Based on the final FDA guidance from May 2019, interchangeability determinations should be based on well-designed dedicated switching trial(s) that include multiple switches (at least 3) and have clinical pharmacokinetics (PK) and pharmacodynamics (PD) (if available) as the primary endpoint.³
 - However, PLANETRA was a trial dedicated to assessing infliximab-dyyb vs Remicade in infliximab naive patients where the primary endpoint was ACR20 at Week 30. It assessed only a single switch as part of an open-label extension where key endpoints were measures of efficacy (e.g. ACR20) at Week 102 and safety, and pharmacokinetics were not measured in this extension. As such, it does not meet the standards laid out by the FDA. To-date, no dedicated interchangeability studies with either infliximab-dyyb or infliximab-abda have been conducted.
- In order to clarify this section to the reader, Janssen suggests keeping the paragraphs regarding PLANETRA and interchangeability together, which would mean to reverse the order of the final two paragraphs.
- Janssen recognizes the importance of real-world evidence and appreciates its inclusion in the report. In the paragraph on the Bulgaria study, we suggest pointing out that this describes the use of infliximabdyyb in naïve patients, which is being shown as supportive data to the PLANETRA randomized study. To complement this real-world evidence in naïve patients, we suggest also to present real-world data in the setting of switching. Janssen recommends referring to a meta-analysis study⁴ previously submitted during the Draft Scoping Document comment period:
 - In a meta-analysis of 62 real world studies of non-medical switching from an originator antitumor necrosis factor (TNF) agent to a biosimilar, the reported annualized discontinuation rate of the biosimilar was 21% and was consistent between rheumatology and inflammatory bowel disease. Among those who discontinued, the switchback rate to the originator biologic among all discontinuers was 62% across all therapeutic areas and 71% in rheumatology specifically. Across all nine studies with control arms, the analysis revealed a statistically significant 18% increase in discontinuations in patients who switched compared with those who did not.⁴

LONG-TERM COST EFFECTIVENESS

Section 4.1, Page 40, Overview:

- Janssen disagrees with limiting the time window to one year in the base case.
- Literature on conducting economic evaluations in health care advocate using appropriate time horizons that reflect the full period over which the costs and effects are captured, which is often over the patient's lifetime.⁵ Previous existing models in RA, including ICER's 2017 model, have used a lifetime time horizon.⁶
- Rheumatoid arthritis is a chronic and debilitating disease often requiring lifelong treatment. Persistence and durability of treatment, as well as the effect of switching, are important when considering treatments.
- Clinical benefits, such as avoiding of acute events and delaying of disease progression, occur over time, and modeling a one-year time frame may miss the full picture of disease modifying treatment benefits.

• Beyond direct costs, it is important to consider the overall burden of disease, including aspects such as disability and compromised productivity. It is important for patients to have access to treatments that will provide efficacy over time and minimize indirect costs of disease.

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6. Institute for Clinical and Economic Review. Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value Evidence Report. Available at: https://icer-review.org/wp-

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November 1, 2019

Institute for Clinical and Economic Review One State Street, Suite 1050 Boston MA 02109 USA

RE: Updated Draft Evidence Report on Rheumatoid Arthritis Therapies

Dear ICER Review Team:

Merck thanks ICER for the opportunity to provide comments on the updated draft evidence report on RA therapies. On May 1, 2019, we sent to ICER our thoughts and suggestions during the review's public input seeking period. Our views expressed in that letter have not changed. In this letter, we would like to comment on three issues identified in the draft report regarding the biosimilar exemplar that concern us.

First, this draft report includes only one biosimilar of infliximab, which we consider insufficient to demonstrate the role of biosimilars as a viable solution to the affordability issues in RA treatment. Inclusion of all relevant biosimilar products in the report is essential to present an intact picture of the biosimilar landscape, provide more complete information, and raise the awareness of all biosimilar options among patients, providers, and payers.

Second, there is a lack of economic analysis on biosimilar in the draft report. Given that the fundamental reason for development of biosimilars is to offer more affordable treatment options (i.e., potentially lower health care costs through competition), such lacking significantly reduces the informativeness of this review for stakeholders who want to look into the potential roles of biosimilars in RA treatment.

Third, the interchangeability discussion regarding biosimilar is premature and should not be a focus of this report, because FDA has not given 'interchangeability' status to any product. We believe the focus of discuss should be on bio-similarities between biosimilars and originators.

We suggest ICER revise the report to address our concerns. We will continue engaging with ICER in its future value assessment efforts.

Sincerely,

JangSur

Fang Sun, M.D., Ph.D. Director, Medical Policy, HTA & Value Assessment The Center for Observational and Real-World Evidence (CORE) Merck & Company, Inc.

November 8, 2019

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

RE: RA Draft Evidence report

Dear Dr. Pearson,

On behalf of Pfizer Inc., thank you for the opportunity to comment on the draft evidence report on JAK inhibitors to treat rheumatoid arthritis. There are six areas we would like to address in our comments:

- 1) DAS28-ESR to DAS28-CRP conversion
- 2) Cost-effectiveness conclusions drawn for tofacitinib without a model
- 3) Time horizon of cost-effectiveness model
- 4) Draft voting questions with lack of model for drugs other than upadacitinib
- 5) General inaccuracies in the report
- 6) Transparency around changing decisions and differences between draft and final reports

In particular, we feel that ICER is using several different methods to assess the products in this review and the entire biosimilar piece is lost as it is a separate topic from the assessment of the JAK inhibitors. This leads to confusion for readers of the report and no easy way to summarize the results for the different therapies in a concise way as each has their own nuances. Pfizer has recommended from the beginning that the use of the DAS28-CRP at three months endpoint was not advisable as it would lead to complications with comparing the various therapies. To date, no peer-reviewed model in the literature has used this approach. While ICER represents this as a lack of data on the part of tofacitinib and baricitinib, in fact tofacitinib has the most robust and longest term clinical data available of the JAK inhibitors. So while tofacitinib lacks the one precise endpoint at one particular timepoint that ICER chose to use for their model, it has a wealth of other clinical efficacy data available to make indirect comparisons. Most of the complications with the model below stem from ICER's decision to work with an endpoint and timepoint that is only available for one therapy rather than selecting a more broadly applicable endpoint and timepoint.

DAS28-ESR to DAS28-CRP conversion

While it is appreciated that ICER attempted to perform some sensitivity analyses around this conversion, the underlying principle here is highly flawed. ICER acknowledges in their own comments that the cDMARD arms showed more variability than the TIM arms between DAS28-ESR and DAS28-CRP but then uses the same conversion for both tofacitinib and the cDMARD

comparator creating a significant amount of bias within the model. This conversion then taints both the comparison of tofacitinib to the cDMARD arm as well as the indirect comparison of tofacitinib to adalimumab as it relies on the tofacitinib to cDMARD comparison. The literature does not support simply using the relative proportion from clinical trials without a model controlling for covariates and ignoring variation in one arm of comparators. Finally, looking into the Appendix where the calculation is described, the method is still not fully transparent or laid out. If all three DAS28-ESR score categories were simply multiplied by 2 or 1.5 then you would end up with over 100% of patients. So it is unclear if the remission category is the only category where 2x is used, the low disease activity is where the 1.5x is used and the high disease activity is simply the remaining patients or if ICER approached this differently. With rounding errors, it is difficult to tell.

<u>Recommendation</u>: Remove this conversion and either select a different endpoint to compare products or restrict the conversation about tofacitinib to the clinical efficacy section.

Cost-effectiveness conclusions drawn for tofacitinib without a model

The report contradicts itself in several places with regards to the comparisons and conclusions around the relative benefit of tofacitinib and adalimumab. The report seems to want to rely solely on clinical data but also mentions using an indirect modeling comparison. Please see four direct quotes below (emphasis added).

Pg 55: "We were **unable to draw a comparison** between tofacitinib and adalimumab in our analyses due to a **lack of comparable efficacy data**...However, we comment on the value of tofacitinib relative to adalimumab **based on the relative cost effectiveness** of these TIMs when compared to conventional DMARDs in their respective trials."

Pg 63: "As stated earlier, we were unable to compare the cost effectiveness of tofacitinib versus adalimumab due to a lack of data. However, we compared the outcomes of the two TIMs relative to their respective conventional DMARD comparators. The different values noted in the tables below for the cDMARD comparator arms directly **reflect outcomes observed in the adalimumab and tofacitinib clinical trials**, respectively."

Pg. 64: "Results from Tables 4.15 and 4.16 demonstrate that the use of adalimumab or tofacitinib compared to conventional DMARDs **results in marginally more QALYs** at one year, at a higher cost."

Pg 71: "**Results from the indirect modeling comparison** of tofacitinib to adalimumab suggest that for the marginal benefit tofacitinib offers, a price much higher than adalimumab may not be justified."

These serve to confuse the reader of the report. On the one hand ICER states that there is not enough data to perform a comparison and is reporting clinical trial data only, but then states that

using an indirect modeling approach they are able to make a comparison. This indirect modeling approach is neither supported by ICER's value framework nor the literature. The literature on network meta-analyses and cost effectiveness modeling suggests that if an underlying network cannot be built, comparisons cannot be made. One cannot do an indirect treatment comparison of an indirect treatment comparison or a naïve comparison via a common comparator.

We would like to emphasize again that lack of the data is not because there is not enough data for tofacitinib but because ICER decided to use an endpoint and timepoint for which no data is available. A wealth of data comparing tofacitinib to adalimumab has been published in peer review journals.

<u>Recommendation</u>: If ICER intends to only compare tofacitinib and adalimumab using head to head clinical trial data, they should restrict this discussion to the clinical efficacy section where they discuss ORAL Standard. They should also refrain from drawing conclusions about the relative cost-effectiveness as it is not being modeled in the same fashion as the upadacitinib and adalimumab comparison and does not align with the published value framework from ICER on how they perform assessments.

If ICER would like to assess the cost-effectiveness of tofacitinib to adalimumab they will need to change the model structure and use a different endpoint and timeframe.

Time horizon of cost-effectiveness model

It is unclear why ICER changed the time horizon of the cost-effectiveness model to 1 year from a lifetime. This approach is not supported by ICER own value framework.

Recommendation: Returning to a lifetime time horizon and performing a sensitivity analysis for the 1 year time horizon.

Draft voting questions with lack of model for drugs other than upadacitinib

Given that the main cost-effectiveness model only addresses upadacitinib versus adalimumab, the other draft voting questions (3,4,7,8, 13, 15, and 16) are no longer appropriate. In particular, questions 13, 15, and 16 reference incremental cost-effectiveness which has not been established in the report and thus these questions should be removed. It is also very confusing that the cost-effectiveness of upadacitinib is compared to adalimumab , while for tofacitinib the comparison is cDMARD. Question 5 should be removed as there is no head to head or indirect evidence provided in the report comparing upadacitinib and tofacitinib for the panel members to consider in their vote. Keeping these questions would set a dangerous precedent that the panel is voting on naïve comparisons of clinical trial data.

<u>Recommendation</u>: Remove any voting questions addressed to the panel that relate to baricitinib or tofacitinib unless there is direct head to head data available as ICER provides no indirect treatment comparisons for these therapies aligned with the literature or their own value framework. If they retain questions where there is head to head data, the questions should be reworded to address the fact that the judgement of the panel is to be based on the clinical trial data alone and using different endpoints by product as the DAS28 conversion is flawed.

General inaccuracies in the report

Upon review, Pfizer identified several inaccuracies in the reporting of clinical data for tofacitinib and infliximab-dyyb. These are listed in Appendix A with their exact location for ease of correction.

<u>Recommendation</u>: Fix transcription errors and inaccuracies in the report regarding tofacitinib and infliximab-dyyb.

Transparency around changing decisions

The genesis of this evidence report has been quite complicated and circuitous. What initially was proposed as a review of the class of therapies to treat rheumatoid arthritis has narrowed to just a review of the JAK inhibitors. While the draft report looks at the clinical efficacy data for all the JAKs, cost-effectiveness is only evaluated for upadacitinib versus adalimumab as the current model is not able to compare the other JAKs. Moreover, the draft evidence report was retracted after five days and then re-released with what appeared to be fairly minor and similar to changes that normally would have been made between the draft and revised evidence report. Along the way, very vague rationale was provided to justify these changes and decisions by ICER. Several of these changes (eg changing the model horizon to one year instead of a lifetime horizon) are directly contrary to ICER's value framework. Any deviation from the value framework should be strongly justified. Additionally, while ICER does state that draft evidence reports are just that, by releasing a press release they invite media comment on the draft reports which may turn out to be inaccurate and create a wrong impression about the relative value of the products. Press releases on the current draft evidence report repeated conclusions from the report about tofacitinib that are incorrect given the confusion in how the clinical trial results are represented as cost-effectiveness model results within the report.

<u>Recommendation</u>: Provide more justification on major changes in scope of reviews and in particular provide stronger justification for changes to reports that deviate from the ICER value framework. Additionally, any press releases on draft evidence reports should solely be a call for public comment with corrections released when major changes are made from the draft to the final evidence report.

We thank ICER for their continued consideration of our comments and look forward to the response.

Sincerely,

Rue Centr

Cristina Masseria, MSc PhD Patient and Health Impact (PHI) Methods & Capabilities Lead, Chief Business Office Pfizer Inc. 235 E. 42nd street, New York, NY 10017 Tel: 212-733-5377 <u>Cristina.Masseria@pfizer.com</u>



Appendix A

Original Wording	Page Number	Proposed Change
No biologics have yet been approved as "interchangeable."	45	Replace "approved" to "designated"
The primary endpoint was ACR criteria for ≥20% clinical improvement response (ACR20) at 54 weeks.	45	30 weeks, not 54 weeks
At 54 weeks, there was no difference between groups who met the primary endpoint	45	30 weeks, not 54 weeks
At 54 weeks, there was no difference between groups who met the primary endpoint (74.7% biosimilar vs. 71.3% reference).	45	Change to 74.4% biosimilar vs. 70.1% reference

The proportion of patients achieving ACR50 and ACR70 at 54 weeks was also comparable between groups.	45	Still correct but should be changed to 30 weeks for consistency
Mean decreases in baseline of DAS28-ESR	45	Change "in" to "from"
Treatment-related adverse events were similar between groups (70.5% vs. 70.3% in the reference product)	45	Change "treatment-related" to "treatment- emergent" and "similar" to "similarly reported"
There were no cases of active tuberculosis or lymphoma at 54-week follow-up in either group.	45	From the study: Active TB was reported in three patients (1 %) in the CT-P13 group and no patients in the RP group The manuscript does not mention lymphoma so would recommend removing this mention from the report.
To assess whether the biosimilar is interchangeable with the reference product, studies that compare switching from the reference product to the biosimilar versus continuing on the biosimilar are required.	45	The FDA requirements require a multiple switch study. The PLANTRA study does not meet this definition so would recommend removing this sentence
In an extension of the PLANETRA study, 305 of the 455 patients who completed the study enrolled into the extension study	45	Change "305" to "302"
The primary outcomes were ACR20, ACR50, and ACR70 at week 102.	46	LTE studies have no primary endpoint, propose changing to: "Efficacy assessments were made at baseline and at weeks 14, 30, 54, 78 and 102. Efficacy endpoints included the proportion of patients meeting ACR20, ACR50 and ACR70, among others."

Response rates for maintenance versus switch groups were 71.7% versus	46	Insert "at week 102" after response rates to clarify with the change to the prior sentence
Similar proportions of patients reported treatment- related adverse events	46	Replace "related" with "emergent"
Rates of latent tuberculosis were similar to those seen during the main trial and there were no cases of lymphoma.	46	Remove mention of lymphoma cases as this was not reported in the manuscript
Infliximab-dyyb was approved as a biosimilar by the FDA, but it has not yet been approved as interchangeable.	46	Replace "approved" with "designated"
Table 3.1 NR DAS28-ESR data change from baseline	33	 ORAL Standard Month 3 Change from BL in DAS28-4(ESR) for tofa 5 mg BID + MTX is shown in Supplemental Appendix Figure S4. It's -1.7 units. ORAL Strategy Standard Month 3 Change from BL in DAS28-4(ESR) for tofa 5 mg BID + MTX is shown publication Figure 3. It's -2.2 units. ORAL Scan Month 3 Change from BL in DAS28-4(ESR) for tofa 5 mg BID + MTX is shown in Supplemental Appendix Figure 2. It's -1.8 units. Pooled csDMARD-IR from Charles-Shoeman et al. 2016: ORAL Standard Month 3 Change from BL in DAS28-4(ESR) for tofa 5 mg BID + MTX is shown in Figure 2. It's -1.9 units v0.78 for PBO.

as well as DAS28-CRP <3.2 (45% vs. 29%) and CDAI ≤2.6 (13% vs. 8%).3	35	CDAI cutoff for SELECT-COMPARE is 2.8 not 2.6
Table 3.4	38	Pooled tofa trials from Charles-Shoeman et al. paper is missing the change from BL in HAQ-DI: PBO = -0.09; tofa 5 mg = -0.31

Sandoz, A Novartis Division

Submitted VIA ELECTRONIC SUBMISSION at publiccomments@icer-review.org

November 8, 2019

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

RE: Draft Evidence Report

Dear Sir or Madam,

Sandoz, A Novartis division, is submitting this letter to the Institute for Clinical and Economic Review (ICER) in response to the Draft Evidence Report that was released on October 11, 2019.¹

We hear a lot about the problem of skyrocketing healthcare costs, but few are doing something about it. We believe that biosimilars are one solution to address healthcare costs and give more patients suffering from rheumatoid arthritis access to safe and effective disease modifying medications.

Biosimilars can help provide millions of patients more affordable and accessible treatments. They create the potential to save the US healthcare system \$54 billion over 10 years.² The cost of biologics reached \$120 billion in 2017, but if all approved biosimilars had been marketed in a timely manner, Americans could have saved \$4.5 billion.^{3,4} An estimated 1.2 million US patients could gain access by 2025 as the result of biosimilar availability – with an added benefit to female, lower income and elderly individuals.⁵

Stakeholders can trust that biosimilars have the same efficacy and safety profile for patients as their reference biologics. They are FDA-approved medicines that went through a rigorous development and testing process.^{6,7} In a systematic literature review of 90 studies of 7

⁶ US Food and Drug Administration. Biologic product definitions.

¹ ICER RA Update: Draft Evidence Report. https://icer-review.org/wp-content/uploads/2019/03/ICER_RA_Draft_Evidence_Report_101119.pdf

² Mulcahy AW, Hlávaka JP, Case SR. Biosimilar cost savings in the United States: initial experience and future potential. Santa Monica, CA: Rand Corporation, 2017. https://www.rand.org/pubs/perspectives/PE264.html.

³ IQVIA Institute for Human Data Science. Medicine use and spending in the US: a review of 2017 and outlook to 2022. https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022.

⁴ U.S. Food and Drug Administration. Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilar Action Plan [press release]. July 18, 2018.

⁵ The Biosimilars Council. Biosimilars in the United States: providing more patients greater access to lifesaving medicine.

http://biosimilarscouncil.org/wp-content/uploads/2017/09/Biosimilars-Council-Patient-Access-Study-090917.pdf.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologic Applications/Biosimilars/UCM581282.pdf. Accessed December 14, 2018.

⁷ US Department of Health and Human Services. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. April 2015. https://www.fda.gov/downloads/drugs/guidances/ucm291128.pdf. Accessed Dec 14, 2018.

biosimilars covering 14 disease states and 14,225 patients, no new safety or efficacy concerns were detected.⁸

Sandoz is the first to bring biosimilars to US patients and the first US success story.⁹ Biosimilars may enable more patients to access advanced biologic medicines earlier and offer significant savings for overburdened health systems. We have 35+ years of biologic development, 20 years of biosimilar development and 10+ years of biosimilar commercialization and patient experience.^{10,11}

We appreciate the opportunity to provide comments on the Draft Evidence Report.

Summary of Coverage Policies and Clinical Guidelines

Biosimilars, including infliximab-dyyb, face various challenges to patient access. Sixty percent of FDA approved biosimilars are not available in US market, such as Sandoz biosimilar ErelziTM (etanercept-szzs) that received FDA approval more than three years ago. For those FDA approved biosimilars that are available in the US, market adoption has been slow with some exceptions.¹²

Many obstacles for biosimilars in the US exist along the path that begins with discovery and development; continues with the process of obtaining regulatory approval; and ends with patients accessing their biosimilar for treatment.

Contributing causes include lack of education and awareness about the benefits of biosimilars and coverage and reimbursement strategies that disadvantage biosimilars.

Comparative Clinical Effectiveness

We applaud ICER for including a biosimilar in the comprehensive list of targeted immune modulators with FDA indications for RA. But, we respectfully request that ICER review the clinical evidence for an additional biosimilar, ErelziTM (etanercept-szzs). This clinical evidence includes EQUIRA and EGALITY.^{13,14,15} Etanercept is one of the two more frequently used biologics for patients suffering from rheumatoid arthritis. Additionally, ErelziTM was approved by

⁸ Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. Drugs. 2018; 78(4):463-478.

⁹ US Food and Drug Administration. FDA approves first biosimilar product Zarxio [press release]; March 6, 2015.

https://wayback.archiveit.org/7993/20171105050630/https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm43 6648.htm. Accessed 7, 2018.

¹⁰ Rios, M. A decade of microbial fermentation. http://www.bioprocessintl.com/upstream-processing/fermentation/a-decade-ofmicrobial-fermentation-331179. Published June 1, 2012. Accessed October 30, 2018.

¹¹ US Food & Drug Administration. FDA Oncologic Drugs Advisory Committee Meeting. Zarxio® (filgrastim). January 7, 2015. https://wayback.archive-itorg/7993/20170405222933/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting Materials/Drugs/OncologicDrugsAdvisoryCommittee/UCM428782.pdf. Accessed August 3, 2018.

¹² Forbes. "Biosimilars Continue To Exhibit Market Failure." July 11, 2019. Available: http://bit.ly/2xGIJ7q

¹³ Lll Matucci-Cerinic M, et al. RMD Open 2018 reports the results for treatment period 1 (Treatment period 1; up to 24 weeks) https://mdopen.bmj.com/content/rmdopen/4/2/e000757.full.pdf Accessed October 25, 2019.

¹⁴ Matucci-Cerinic M, et al. Ann Rheum Dis 2018;77(Suppl): A609; EULAR abstract and poster FRI0129 (Treatment period 2, Weeks 24–48).

¹⁵ Griffiths CEM et.al. The EGALITY study. *Br J Dermatol.* 2017;176(4):928-938. <u>https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.15152</u>. Accessed October 25, 2019

the FDA over 3 years ago and the European Medicines Agency in June 2017, with patients in the EU benefitting from treatment. ^{16,17}

We once again recommend that when ICER evaluates the clinical evidence of biosimilars it must be taken in context with the totality of the evidence. A recent review by Coory and Thorton that applied the GRADE evidence criteria to biosimilar trastuzumab found that the totality of the evidence would be categorized as high quality evidence. However, if the randomized trials were evaluated in isolation from the other studies, it could be mistakenly rated as medium-to-low quality. ICER should utilize the same approach as these authors when evaluating the evidence from biosimilars.¹⁸

In ICER's discussion of Biosimilars for RA on pages 37-38, we disagree that significant cost reductions have not been observed in the US. Savings have been realized by patients, health systems, integrated delivery networks and payers when switching to biosimilars. For example, Yale New Haven Health System, Robert Wood Johnson Barnabas Healthcare System and Carolina Blood and Cancer Care realized savings when switching to Zarxio[®].^{19,20,21,22}

Long-Term Cost Effectiveness

We appreciate the current challenges with doing detailed economic analysis for biosimilars.

In the future, we strongly recommend that biosimilar(s) be included in the detailed economic analysis, along with the other interventions, because the primary value of biosimilars rests in providing increased savings and access to biologic treatments. Additionally, the introduction of biosimilar competition to the market impacts the relative pricing of competing biologics in a drug class.

Biosimilars have the same efficacy and safety as their reference biologic but they differ in cost. Therefore, the inputs for the biosimilar for an economic analysis would be the publicly available cost data and the efficacy and safety data of the reference biologic.

Also, in the future, we recommend that the biosimilar evidence paradigm be included in ICER's Value Assessment Framework in order to help assess the clinical and economic value of interventions.

¹⁶ FDA News Release. FDA approves Erelzi, a biosimilar to Enbrel. <u>https://www.fda.gov/news-events/press-announcements/fda-approves-erelzi-biosimilar-enbrel</u> Accessed November 8, 2019.

¹⁷ European Medicines Agency. European Public Assessment Report for Erelzi.

https://www.ema.europa.eu/en/medicines/human/EPAR/erelzi Accessed November 8, 2019.

¹⁸ Coory M and Thorton K. Randomised clinical endpoint studies for trastuzumab biosimilars: a systematic review. Breast Cancer Res Treat. 2019 Apr 12

¹⁹ Data on file. RŴJBH Raw Sales Data. Sandoz Inc. March 2018.

²⁰ Evans, M. Bamabas and Robert Wood Johnson sign deal to form biggest New Jersey health system. Modern Healthcare Website. <u>http://www.modemhealthcare.com/article/20150714/NEWS/150719965</u>. Published July 14, 205. Accessed October 5, 2018.

²¹ Davio K. Oncologist sees biosimilars playing a role in the oncology care model. The Center for Biosimilars Website. Available at: http://www.centerforbiosimilars.com/news/oncologist-sees-biosimilars-playing-a-role-in-the-oncology-care-model. Published April 12, 2018. Accessed June 11, 2018.

²² Leber MB, Abdelghany O, Miller L. Biosimilar adoption: health system challenges and strategies for success. Poster presented at: 2016 Vizient Clinical Connections Summit, Dallas, TX, September 29, 2016.

In closing, biosimilars may enable more patients to access biologic medicines earlier and offer significant savings for patients and overburdened healthcare systems.^{23,24}

Stakeholders supporting biosimilars will be part of the solution in offering patients high quality care at a more affordable price, creating a more sustainable system for patients now and for the future.²⁵

We want to reiterate our appreciation to ICER for the opportunity to provide comments on the Draft Scoping Document. If any questions should arise about our comments, please feel free to contact us.

Sincerely,

Thian to

Edward Li PharmD, MPH Associate Director, Health Economics & Outcomes Research Sandoz

Kellie Calderon MD Executive Director, Head of Immunology Medical Affairs Sandoz

²³ IQVIA Institute for Human Data Science. Medicine use and spending in the US: a review of 2017 and outlook to 2022. https://www.iqvia.com/institute/reports/medicine-use-and-spending-in-the-us-review-of-2017-outlook-to-2022.

²⁴ U.S. Food and Drug Administration. Remarks from FDA Commissioner Scott Gottlieb, M.D., as prepared for delivery at the Brookings Institution on the release of the FDA's Biosimilar Action Plan [press release]. July 18, 2018.

²⁵ McBride A, Campbell K, Bikkina M, MacDonald K, Abraham I, Balu S. Cost-efficiency analyses for the US of biosimilar filgrastim-sndz, reference filgrastim, pegfilgrastim, and pegfilgrastim with on-body injector in the prophylaxis of chemotherapy-induced (febrile) neutropenia. J Med Econ. 2017;20(10):1083-1093.



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November 8, 2019

Steven Pearson, MD, MSc President Institute for Clinical and Economic Review 87 Kilby Street Boston, MA 02109

Re: Institute for Clinical and Economic Review (ICER) Report on Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value

Dear Dr. Pearson:

The American College of Rheumatology (ACR), representing over 9,500 rheumatologists and rheumatology professionals, appreciates the opportunity to respond to ICER's draft evidence report on Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value.

The ACR is an active supporter of comparative effectiveness research (CER) as we believe this type of research has the potential to inform individual physician and patient decisions about the relative value of diagnostic and therapeutic options. We appreciate ICER undertaking this important work and continuing to help address the important issue of cost and value in treatment of patients with Rheumatoid Arthritis (RA).

The ACR appreciates ICER's detailed elucidation of various payers' utilization management pathways related to the drugs discussed in this report. We strongly encourage ICER to point out where these pathways are not in line with FDA approval, ACR guidelines, and/or best practices and where step therapy criteria are more restrictive than the drugs' FDA indications. Specifically, this report mentions requiring failure of more than two tumor necrosis factor (TNF) antagonists before access to a janus kinase (JAK) inhibitor or failure of multiple JAK inhibitors prior to using a TNF antagonist. This prioritizes the rebate status of treatments over their clinical appropriateness, which may thereby increase overall costs by imposing upon providers an obligation to prescribe first a drug(s) they believe is less likely to be effective for an individual patient. We appreciate ICER's mention of how utilization management can have a negative impact on rheumatoid arthritis disease activity, and we also encourage a review of the overall costs imposed by restrictive utilization management strategies and the resulting prior authorizations. These additional costs have a significant impact on our health care system and should be considered and potentially factored into a drug's QALY rating.

We appreciate ICER's focus on ensuring a high level of quality data for this report; however, we are concerned that the duration of the studies is relatively short and feel longer-term studies and



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outcomes data for JAK inhibitors are needed. The cost-effectiveness analysis for upadacitinib (Rinvoq) would also be more impactful if the report also included a similar analysis for additional drugs.

The ACR would like to see more emphasis placed on the role for biosimilars in the cost and value discussion. We are concerned that comparing cost effectiveness to adalimumab (Humira) alone does not provide sufficient context. Although the report mentions biosimilars, their overall potential impact is greatly minimized. Reviewing Medicare payment limits, which are based on average sales price (ASP) data, shows the extent to which biosimilars are helping to reduce cost for infliximab. As shown in the table below, the payment limit of the originator drug, infliximab (Remicade), has dropped 24 percent since early 2018. Biosimilars infliximab-dyyb (Inflectra) and infliximab-abda (Renflexis) have experienced a similar decrease. In comparison, prices of both certolizumab (Cimzia) and abatacept (Orencia) –biologic drugs without direct competition from a biosimilar product –continued to climb during this period, increasing by nearly four percent and eight percent respectively. The ACR shares ICER's desire to see maximal value for cost in the targeted immune modulator (TIM) space, and we believe ICER could help promote uptake of biosimilar use, where appropriate, if more detailed cost-effectiveness data in light of these newer price points, were part of this report.



Source: <u>https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Part-B-</u> Drugs/McrPartBDrugAvgSalesPrice/index.html



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Lastly, we greatly appreciate ICER's efforts to include several rheumatologists as expert editors of this report. It is our hope that ICER will continue to solicit feedback from clinical experts and, in the future, consider including them in the process before the model structure is developed so they can provide input throughout the project.

The ACR appreciates the opportunity to respond to this report and your consideration of our comments. Please contact Rachel Myslinski, Vice President of Practice, Advocacy and Quality at <u>rmyslinski@rheumatology.org</u> or (404) 633-3777 if you have questions or if we can be of assistance.

Sincerely,

I March D=

Paula Marchetta, MD, MBA President, American College of Rheumatology





Institute for Clinical and Economic Review 2 Liberty Square, 9th Floor Boston, MA 02109 November 8, 2019

RE: Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness and Value; Condition Update; Draft Evidence Report

To Whom it May Concern:

The Arthritis Foundation, representing over 54 million American adults and 300,000 children with arthritis, is pleased to offer comments to the Institute for Clinical and Economic Review (ICER) on its draft evidence report for targeted immune modulators for rheumatoid arthritis (RA) condition update.

The Arthritis Foundation appreciates the opportunity to comment on the 2017 review and the present revision. ICER's efforts to improve its methodologies are appreciated and reflect a responsiveness to prior comments. We note, however, that some of our concerns from the 2017 review remain and complicate interpretation of the results of the analysis. These include: a narrow study analysis that did not include a representative sample of people with RA, and therefore was not relevant to all people with RA; conclusions reached based on inadequate performance measures; the reliance on quality-adjusted life years (QALYs) which is inappropriate for this disease population; and an absence of real-word evidence and patient experience data in the final analysis.

Below please find our specific comments.

Background

We appreciate the discussion of Arthritis Foundation involvement in the 2017 review. We believe our survey results showing the difficulty in finding effective treatments coupled with the high rate of administrative burden led to ICER's conclusion that utilization management protocols like step therapy are not appropriate for all patients. Subsequent Arthritis Foundation surveys and focus groups have reinforced these findings and we encourage ICER to reiterate this conclusion in its final report.

Coverage Policies and Clinical Guidelines

The coverage section of this draft report talks extensively about the difficulty in accessing some of these treatments. In particular, we are concerned that among major US commercial payers, many patients are required to fail on the reference product before they can access the biosimilar. This is one of many examples of misaligned incentives that can ultimately disadvantage the patient. We are curious how ICER will account for market practices like this in its final review.





Comparative Clinical Effectiveness

While we understand the limitations in clinical trial data, we remain concerned that ICER is only looking at moderate to severe patients, and those who have not had adequate response to conventional DMARDs. We appreciate the recognition that Patient Reported Outcomes are important in assessing clinical effectiveness, and we encourage ICER to work closely with patient organizations like the Arthritis Foundation that are collecting this data. Our Live Yes! INSIGHTS program is designed to collect data from arthritis patients based on the PROMIS 29 measure set. The selection of these measures is backed by a Nominal Group Technique process with patients that allowed patients living with arthritis to compare Quality of Life tools in their relevancy to a life lived with arthritis. To-date we have received over 20,000 survey responses and are finalizing the first reports on our initial findings.

ICER rightly notes the paucity of random control trial evidence and the fact that clinical guidelines have changed. We encourage ICER to work closely with the American College of Rheumatology in advance of the final report publication to ensure updated clinical guidelines are appropriately incorporated in the review.

Long-term Cost Effectiveness

We appreciate that ICER is modeling long-term cost effectiveness and recognizes the importance of aligning the model with the treat-to-target paradigm, focusing the primary model on intention-to-treat and treat-to-target analysis. It must be noted that, while widespread, adoption of treat-to-target is incomplete, and practiced at less than half of rheumatology clinics. This reflects the variability in practice across the community, and should be noted as a complexity in interpreting the results of the ICER model.

Overall, we remain concerned that the choice of therapy RA represents is not a singular event but rather an iterative "best choice" scenario over many decades of life. RA patients will cycle over many therapies for decades, and the ultimate outcomes represent the summed experience on many drugs. Such outcomes are not captured in two-year clinical trial data. Likewise, payer decisions are incentivized by knowledge that the average patient remains on a given policy for under 3 years. The reliance of ICER on such short-term data supports this incentive, at the expense of consideration for patients' long-term health. While ICER has attempted to model treat-to-target approaches in the current model, the data referenced reveal the underlying limitations of the present understanding of clinical practice. We remain concerned that the analyses as presented do not adequately acknowledge the uncertainty in the current literature.

The Arthritis Foundation maintains that while the initial ICER review advanced a systematic process for comparative pharmacoeconomics, many concerns remain about the core methodologies and their applicability to chronic disease states, particularly RA. Concerns in this draft evidence report include:





- The target population includes only severe disease activity, aligning with available clinical trial populations from studies used in this review. As in our previous comments, we believe younger patients and those with early/mild RA should be included as they likely differ in the secondary prevention benefits they receive from long term treatment.
- ICER uses a hypothetical homogenous population, which may be consistent with clinical trial populations, but it is not consistent with the majority of patients with RA. In our scoping document comments we strongly recommended that ICER run scenarios for particular subgroups based on biomarker results, or other patient or disease characteristics, and that this would be informative to potential decision-makers for both understanding the variance in value across treatment strategies and for preventing the harm that could be caused by gross oversimplification of complex sets of outcomes.
- It remains unclear as to how ICER will account for the frequent occurrence of comorbidities in this population.
- We remain concerned about the reliance on QALYs, which we and nearly all other public commentators this and other chronic conditions, have noted is an insufficient method to determine cost effectiveness, particularly among patients with chronic diseases.
- ICER costs are based on wholesale drug costs that may differ practice-to-practice and between government and private insurers. ICER should provide contextualization in their report to take into account that actual costs may dramatically over or underrepresent the costs actually incurred by provider.

Contextual Considerations

As we have stated in the past, contextual considerations are essential to truly assessing the impact of a treatment on a patient in real-world settings, and in measuring their overall quality of life. We appreciate inclusion of factors like caregiver burden and ability to work, and the overall recognition by ICER that these factors are important. We urge ICER to continue working with patient groups and other stakeholders to build contextual considerations as a core component of the overall methodology and weight them appropriately.

Conclusion

While the methods used in this review are an improvement upon the methods used in the 2017 report, there are still concerns that must be addressed, including the use of QALYs, the lack of RWE, weighting of contextual considerations, the lack of accounting for heterogeneity of disease and co-morbidities, and current market structures that impact what treatments patients have access to. We urge ICER to continue working with broad groups of stakeholders, including patient and provider groups, throughout this review process.

We look forward to opportunities to engage further throughout the review process. Please contact Anna Hyde, Vice President of Advocacy and Access, at <u>ahyde@arthritis.org</u> with any questions.

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November 8, 2019

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

Dear Dr. Pearson,

The Partnership to Improve Patient Care (PIPC) appreciates this opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft evidence report for treatments for rheumatoid arthritis. As you know, rheumatoid arthritis (RA) is a is a severely painful disease that impacts 1.3 million Americans.¹ Arthritis is the leading cause of disability among adults in the United States.² Given the severity of the disease, and the large patient population, we urge you to evaluate these treatments with the perspectives of patients at the center and using methodologies that will improve, not inhibit, the ability of patients to access treatments that they need. We are hopeful that ICER will take steps to address the shortcomings of its prior reports, which largely omit patient input, ignore the heterogeneity of the patient population, and prioritize RCT data over real-world evidence. We hope you will consider our specific concerns and recommendations below.

ICER Continues to Rely on a Population Perspective Ignoring the Heterogeneity of **Rheumatoid Arthritis Patients**

RA is a disease for which treatment is very specific to an individual, as was emphasized by many commenters on the original ICER report on RA in 2017. Therefore, we urge ICER to take steps to more accurately capture the actual RA patient population by using a micro-simulation model to run a series of different patient scenarios and assess cost-effectiveness for a set of atypical patients. This is especially important due to the range of patient types with this disease. Specifically, the variation in both the severity of the symptoms and the amount of time patients have been managing the disease has implications for a treatment's impact on individuals. ICER could then present the results as a range and highlight the importance of individual decisionmaking and the key drivers of value across treatment options for different types of patients. Using a population average in this report likely will lead to the unintended consequence of it being representative of no one, rather than everyone.

The literature is very clear that RA is a disease with significant heterogeneity, requiring that treatment decisions must incorporate patient-specific factors. The European League Against Rheumatism (EULAR) states, "Treatment decisions should be determined by patient-specific

¹ Rheumatoid Arthritis Support Network. RA Facts. Accessed October 22, 2019.

² The Arthritis Foundation. Arthritis Facts. Accessed October 22, 2019



factors as well as disease activity."³ The American College of Rheumatology (ACR) echoes this, noting, "[a]s an overarching principle, ACR guidelines note that treatment decisions should be made through a shared decision-making process between the clinician and patient, and that any treatment decision should factor in patient preference and comorbidities."⁴

Despite this overwhelming evidence of the need for treatment decisions to reflect individual patients and the heterogeneity among RA patients, ICER finalized its prior RA model based on just one homogenous population: adults in the US with severely active RA with inadequate response to conventional DMARDs and naïve to TIM therapy. By contrast, we believe running scenarios for particular subgroups based on - at a minimum - objective measures such as biomarker results would be more informative to decision-makers in terms of understanding the variance in value across treatment strategies and the potential value of targeting based on predictive biomarkers.

ICER Continues to Request Input from Patients but Neglects to Include it Meaningfully in Reports

In the feedback patient and advocacy groups have already provided to ICER about what was most important to them in a treatment for RA, three common themes emerged.

- 1. Patient experiences of the disease are very individual, and the effectiveness of different treatments is very specific to individuals given their disease type and associated comorbidities.
- 2. Patients emphasized the long-term nature of the disease and encouraged a long-term perspective in evaluating its treatments.
- 3. Patients highlighted the importance of patient-reported outcomes and went as far as to offer to help ICER include these outcomes in the report and model.

Though ICER acknowledged these patient comments, it made the ultimate decision to omit them from the model.

Many stakeholders commented on the heterogeneity of RA patients and provided ICER with detailed suggestions for how to capture this in its model. For example, the Arthritis Foundation suggested ICER run "scenarios for particular subgroups based on biomarker results, or other patient or disease characteristics." As noted above, despite overwhelming evidence of the need to reflect patient specificity and heterogeneity across the syndrome, ICER finalized a model based on just one homogenous population: adults in the US with severely active RA with inadequate response to conventional DMARDs and naïve to TIM therapy."

³ Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases. 2014;73(3):492-509.

⁴ Singh JA, Saag KG, Bridges SL, Jr., et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.



Patients also consistently made the point that it is important to capture the long-term nature of RA, emphasizing that it is important to maintain a long-term perspective on treatment since patients' experience and treatments can change substantially over the course of the disease. Though ICER acknowledged this feedback, it used a model that works on a 3-month cycle of effectiveness and assumed no sequencing. It simply assumed that discontinuation or treatment failure leads to palliative care with no chance of remission, and the base case model runs for just one year. This model loses all of the nuance that patients and advocates encouraged ICER to capture by looking at the long-term nature of the disease.

Finally, patients and advocacy groups highlighted the extreme importance of incorporating disease-specific patient-reported outcomes (PROs). Global Healthy Living Foundation went so far as to offer a patient-reported outcomes registry of nearly 20,000 people with arthritis, which CreakyJoints created through funding from the Patient-Centered Outcomes Research Institute (PCORI). The registry, Arthritis Power, collects real world data and patient reported measures that can be combined with clinical and payer data to provide a picture of the real-world experience of RA patients. Instead of incorporating disease-specific PROs in their model, ICER used a Markov model built around transitions and health states designed as proxies of disease activity measures (specifically DAS28). Similarly, the outcomes of the model are expressed primarily in terms of disease response rates (ACR20, ACR50 ACR 70, and HAQ-DI). ICER's model directly contradicts what the patient advocates suggested would be the most appropriate way to evaluate the value of new therapies for RA in practice.

ICER Ignores Disease-Specific Patient Reported Outcomes (PROs) in Favor of Generic **PROs that Crosswalk Easily into the QALY**

Building on the previous point about lack of inclusion of patient-specific PROs, it is important to remember the, often, significant differences between the disease-specific and generic PRO. The primary purpose of the disease-specific PRO is to maximize the sensitivity of the tool to the health-related quality of life of the specific patient and disease under investigation. By contrast, the primary purpose of the generic PRO is to compare across diseases - for which shared symptom relevance may be very low – and to fit into pre-configured domains for translation into the discriminatory QALY measure. A major problem with generic instruments is that they are not designed to capture areas of concern to specific patient populations. Asking patients to answer questions that are irrelevant is likely to alienate respondents and increase the potential for missing or inaccurate responses. Second, they are likely to miss issues that are a specific feature of the disease under study. As a result, generic scales lack the responsiveness needed to measure change associated with effective treatment.5

Generic PROs are relatively dated. Most generic PROs are derived from a set developed in the 1970s. The relative importance and the language used around domains have changed markedly

⁵ McKenna SP. Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. BMC medicine. 2011 Dec;9(1):86.



since this time. Furthermore, the generic health status instruments have not benefited from improvements in test construction methodology and scaling techniques.⁶ This is why a combination of disease-specific and generic tools are often recommended for RA.7

Disease-specific tools address those aspects of outcome that are important for a particular patient population, achieved by responses from qualitative interviews with relevant patients and thorough testing of the validity of the item set with new populations of patients. These tools employ methods to ensure that all items actually assess the construct being measured.^{8,9} Consequently, disease-specific instruments possess greater potential for showing differences between competing therapies.

ICER Continues to Prioritize Randomized Clinical Trial Data Over Real World Evidence (RWE) Even with the Existence of Strong RWE

RA is a condition that has substantial, high-quality RWE. The network meta-analysis used to quantify absolute treatment effects in this study is still limited to trial data even though the vast majority of agents being evaluated have been in use for years and are captured in available RWE. There have been a number of studies built around the use of real world evidence both in RA more generally¹⁰ and in the evaluation of JAK inhibitors as a class more specifically.¹¹ There are even examples of where RWE has been incorporated into network meta-analyses for RA.¹² Other studies confirm how important RWE is in the evaluation of treatment in RA patients. The populations studied by RA RCTs are often very different than those populations of RA patients in the real world. RCT populations tend to be younger, tend to have had the disease for less time and have had fewer alternative treatments than patients in the real world.¹³

⁶ Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical care. 1992 Jun 1:473-83.

⁷ Lubeck DP. Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics. 2004 Sep 1;22(1):27-38.

⁸ Gilworth G, Chamberlain MA, Bhakta B, Haskard D, Silman A, Tennant A. Development of the BD-QoL: a quality of life measure specific to Behcet's disease. The Journal of Rheumatology. 2004 May 1;31(5):931-7.

⁹ Keenan AM, Mckenna SP, Doward LC, Conaghan PG, Emery P, Tennant A. Development and validation of a needs-based quality of life instrument for osteoarthritis. Arthritis Care & Research: Official Journal of the American College of Rheumatology. 2008 Jun 15;59(6):841-8.

¹⁰ Svedbom A, Storck C, Kachroo S, Govoni M, Khalifa A. Persistence with golimumab in immune-mediated rheumatic diseases: a systematic review of real-world evidence in rheumatoid arthritis, axial spondyloarthritis, and psoriatic arthritis. Patient preference and adherence. 2017;11:719.

¹¹ Caporali R, Zavaglia D. Real-world experience with tofacitinib for treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2018 Aug 29.

¹² Jenkins DA, Martina R, Dequen P, Bujkiewicz S, Abrams K. The Added Value of Real-World Evidence to Connect Disconnected Networks for Network Meta-Analysis: A Case Study in Rheumatoid Arthritis. Value in Health. 2016 Nov 1;19(7):A393.

¹³ Kilcher G, Hummel N, Didden EM, Egger M, Reichenbach S, GetReal Work Package 4. Rheumatoid arthritis patients treated in trial and real world settings: comparison of randomized trials with registries. Rheumatology. 2017 Nov 14;57(2):354-69.



Multiple parties have been encouraging the greater use of RWE in cost effectiveness modeling including a host of prominent health economists,¹⁴ the Food and Drug Administration,¹⁵ and ICER's lodestar, NICE.¹⁶ These groups have all echoed the point that real world evidence is far more likely to generate results that are relevant to true practice and real world effectiveness than trial data alone, yet ICER continues - even in this instance - to undertake evidence metaanalyses only from trial data.

Use of Utility Data Derived from Heath Assessment Questionnaire Scores Leads to a **Dilution of Effects of Treatment**

The use of utility data derived from Health Assessment Questionnaire (HAQ) scores, which in themselves are derived from changes in disease response rate, indicates a greater risk of dilution of effects in over-translation across sets of outcomes. The more steps of translation there are, the more loss of variance in samples can lead to underestimation of the effects of treatments. The choice may have been understandable in a context of limited use of patient reported outcomes in RA treatment trials, but there is significant available data of this type.

Another concern is the use of the Wailoo et al (2008)¹⁷ algorithm for translating HAQ to utilities, and not those developed more recently in Hernandez et al (2012).¹⁸ Multiple publications have highlighted that the latter is more accurate and has been used in more recent models.¹⁹ Looking at figure 2 in Hernandez et al (2013), 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 model is likely to underestimate the positive impacts of treatment.

An additional concern with the HAQ translation is how it is used to generate estimates of mortality probability. The ICER model concentrates on the relationship between levels of HAQ and mortality but there is evidence that levels of change in HAQ from baseline decreases the probability of mortality.²⁰ Exclusion of this factor may underestimate the value of successful treatment in the ICER model.

¹⁴ Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103. ¹⁵ https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

¹⁶ https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869 ¹⁷ Wailoo AJ, Bansback N, Brennan A, Michaud K, Nixon RM, Wolfe F. Biologic drugs for rheumatoid arthritis in

the medicare program: a cost-effectiveness analysis. Arthritis & Rheumatism. 2008;58(4):939-946.

¹⁸ Hernandez Alava M, Wailoo AJ, Ara R. Tails from the peak district: adjusted limited dependent variable mixture models of EO-5D health state utility values. Value Health 2012;15:550 61.

¹⁹ Stevenson MD, Wailoo AJ, Tosh JC, Hernandez-Alava M, Gibson LA, Stevens JW, Archer RJ, Simpson EL, Hock ES, Young A, Scott DL. The cost-effectiveness of sequences of biological disease-modifying antirheumatic drug treatment in England for patients with rheumatoid arthritis who can tolerate methotrexate. The Journal of rheumatology. 2017 Jul 1;44(7):973-80.

²⁰ Michaud K, Vera-Llonch M, Oster G. Mortality risk by functional status and health-related quality of life in patients with rheumatoid arthritis. J Rheumatol. 2012 Jan;39(1):54-9.



Conclusion

ICER continues to rely on traditional QALY-based methods that are not suited to the incorporation of real-world evidence and patient perspectives, demonstrated in the lack of incorporation of patient feedback into ICER's models. We urge ICER to follow the lead of organizations that are building patient-centered models for clinical and cost effectiveness that are better suited to incorporating disease-specific patient reported outcomes, heterogeneity within patient populations, and preference to RWE over RCT data where available.

Sincerely,

1 Coelho

Tony Coelho

Chairman, Partnership to Improve Patient Care



November 8, 2019

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

RE: JAK Inhibitors for Rheumatoid Arthritis: Draft Evidence Report

Dear Dr. Pearson:

Patients Rising Now advocates on behalf of patients with life-threatening and chronic conditions to improve their access to vital treatments and services. Access is a matter of quality of life and survival for those patients. To support improved access, we engage stakeholders to foster realistic, people-centered, solution-oriented discussions to create balanced, truthful and equitable dialogues about health care.

We appreciate the opportunity to provide our comments on ICER's October 11th Draft Evidence Report "Janus Kinase Inhibitors for Rheumatoid Arthritis." We are also encouraged that ICER delayed the release of the draft report to revise and update its methodology and data so that the draft report better included "economic modeling with how patients transition between these therapies [evaluated in the report] in the real world,"ⁱ including using "a three month cycle length [for therapy switching] because we understood from clinicians that this more closely aligns with the clinical strategy used in the recommended treat-to-target approach."ⁱⁱ We see this as a positive step for ICER, and indicative that ICER may be trying to better align its work with real-life situations.

Our specific people-focused comments about the draft report are organized below into sections about People-Centered Perspectives; Data and Analytical Uncertainties; and Additional Points. Within those sections we have identified specific questions or points for ICER to respond to with this symbol ».

We would first like to note our concern and confusion about the brief and disconnected discussion of the biosimilar *infliximab-dyyb*. While we appreciate the potential importance of biosimilars for the evolution of the U.S. health care market, the draft report's overview of biosimilars in a "separate section"ⁱⁱⁱ – and additional discussion of *infliximab-dyyb* – simply do not achieve the stated goals that the "biosimilar data [in the draft report] are useful in framing a general discussion about the role of biosimilars and interchangeability status in RA,"^{iv} and that "this section [in the draft report] will inform a discussion of biosimilars as part of the policy roundtable at the public meeting,"^v for several problematic reasons:

• First, the science behind the regulatory requirements for biosimilars is quite complicated, including the issues of quality assurance related to intra-batch variance and inter-batch

genetic drift that affect both biologics and biosimilars;

- Second, the overview information provided about biosimilars^{vi} is brief (five paragraphs), and the coverage information about *infliximab-dyyb* compared to the reference biologic^{vii} is superficial and fails to explore the deep, broad, important complexities of the biosimilar situation in the U.S., including patent issues (i.e., so-called "patent thicket"), reimbursement issues that are complicating market penetration of biosimilars in the U.S. (including the so-called "rebate trap"), differential incentives patients and clinicians may be facing because of the benefit structures of various health plans (including Medicare), and different cost-sharing requirements between medical and pharmacy benefits;
- Third, while the draft report is supposed to be about JAK inhibitors for RA, *infliximab-dyyb* is a different class of treatment with label indications for eight different conditions, only one of which is RA.^{viii} Thus, information provided about *infliximab-dyyb* in the draft report is not substantively useful for clinicians, patients, or policy makers;
- Fourth, the draft report states that *infliximab-dyyb* "has not yet been approved as interchangeable," which implies that such approval is pending without citing any information. However, according to news reports, only one product (not *infliximab*) has conducted a switching study, and that study has not been submitted to the FDA;^{ix}
- Fifth, if ICER's intent was to show that for the purposes of the draft report *infliximab-dyyb* is equivalent to the reference biologic, then that could be simply stated in the main section of the draft report, and any supporting information that ICER deems necessary should be provided in an appendix; and
- Sixth, why is the CTAF going to discuss biosimilars?^x And will this discussion be about *infliximab-dyyb* specifically, or a general discussion about biosimilars, which, as we've noted above, is a very complicated matter involving patent law, as well as regulations and various market activities by biopharma companies, private payers, and Medicare?

These problems lead us to conclude that, unlike the deep dives and extensive discussions ICER's reports contain about other topics related to particular treatment options, the draft report's superficial discussion of biosimilars does not contribute to the substance of the draft report. **»We would recommend that ICER delete this information from its report on JAK inhibitors, and if ICER determines that biosimilars are an important issue on which the organization has insights to contribute to the ongoing policy discourse on this issue, then it should create a report specifically about biosimilars, such as it has done for indication specific pricing.^{xi}»**

People-Centered Perspectives

Rheumatoid arthritis (RA) is a serious, complicated, systemic autoimmune disease that is often thought of as simply being a disorder of joints. However, unlike osteoarthritis – which can be viewed as isolated joint damage secondary to injury, overuse, or anatomical problems – RA can cause significant problems in other organs including the cardiovascular system, lungs, and eyes. Therefore, although we recognize that the clinical studies and metrics related to treating RA focus on joint damage (as well as some markers of autoimmunity and inflammation), we urge ICER to expand their person-focused perspectives in the report with greater discussion of those non-osseous manifestations of RA.

The draft report does a respectable job of including people-centered information and perspectives in its description of RA – including the real-life impact uncontrolled RA has for $people^{xii}$ – and

reviewing some patient focused data sources, patient survey information,^{xiii} and caregiver perspectives. However, given that some of that information is dated, we believe it would have been preferable for ICER to work with organizations such as the Arthritis Foundation to conduct new surveys or focus groups to update that information since there are new treatment options for RA and the overall contours of the U.S. health care system continue to evolve.

Overall, it is very good news that the JAK inhibitors provide clinical benefit for people with RA, e.g., "JAK inhibitors plus conventional DMARDs achieved low disease activity and remission at three and six months by multiple measures of disease activity (Appendix D) compared with conventional DMARDs alone"^{xiv} – at essentially the same price. And similarly, that "upadacitinib resulted in patients spending approximately one more month on average (over the course of a year) in remission compared to the use of adalimumab,"^{xv} which is an outstanding improvement from a patient's perspective. However, we note that the minimal price/cost differential in the draft report does not necessarily translate into similar costs for patients because – as you know – health plans' formulary coverage and co-insurance tiering can result in very large cost changes for patients.

On that topic, we appreciate the discussion about how "patients fear restrictions on access to certain types of drugs, as well as more general restrictions (e.g., stopping and re-starting therapy, requirements to repeat step therapy after switching health plans, etc.),"^{xvi} but would like to note that this is primarily a situation faced by people in the U.S., and that Boytsov et al.,^{xvii} found 34% of RA patients were in plans with access restrictions, and 70% of those plans had step therapy requirements – which was associated with decreased likelihood of treatment adherence and proxies for reduced treatment effectiveness. Such access restrictions are particularly problematic for people with RA and similar complex chronic conditions when they switch health insurance plans, which can occur with change of employment, by relocating to a different geographic area, or by aging into Medicare. And on a related note, we think that ICER should note that the copay assistance programs (including coupons)^{xviii} are not available to people on Medicare.

And we appreciate the brief discussion of the benefits to people with RA of having treatment options that are oral and do not require visits to a clinician's office. With the ongoing shortage of qualified clinicians in rural and other underserved areas, the ability of patients to receive their care without additional access barriers is an important consideration of value to patients.

Related to access, and patient's needs and perspectives, we are concerned that the Societal Perspective analysis only includes productivity costs. Such a narrow analytical framework might be appropriate if "society" is only concerned with economic output, but we believe that society – and its perspectives – has a much broader view that includes people's non-working lives. For example, if the societal perspective of government action were only to include direct productivity considerations, then parks and the arts would not receive any funding, and health care for non-working individuals would be devalued. We believe this perspective of ICER is consistent with its overall reliance on the QALY as a basic analytical tool, which as we and others have noted, discounts such important societal perspectives.

»In this vein we would like ICER to specifically comment on why it chose not to include the

following societal perspective parameters listed in Appendix E that are important to people and society.»

- Patient Time Costs
- Unpaid Caregiver Time Costs
- Transportation Costs
- Cost of Uncompensated Household Production
- Cost of Social Services
- Impact of Intervention on Educational Achievement

In addition, because ICER's intended audience appears to be public policy decision makers, we suggest that ICER's reports present the Societal Perspective first, and then present its "Base Case" scenario as a subset of the Societal Perspective analysis. **We would appreciate hearing ICER's thoughts on presenting its analyses in that order.**»

And lastly, we want to note that the "independent committee of medical evidence experts" that will be reviewing ICER's analysis about JAK inhibitors^{xix} for use in people with moderate-to-severe RA contains only one patient advocate – whose area of focus is cancer – and several medical doctors with experience in cardiology, oncology, and neurology, but none with expertise in rheumatology or immunology. We realize that ICER's focus in selecting members for its independent advisory committees is expertise in comparative effectiveness research and cost analysis, but having only one patient representative and failing to include clinicians with expertise in areas connected to the condition under review, presents a clear opportunity for having very skewed perspectives and input, which would seem to be the opposite of ICER's apparent objectives.

Data and Analytical Uncertainties

Because the treatments discussed in the report include many that have indications beyond RA – including tofacitinib, adalimumab and other TIMs as well as methotrexate, which is indicated not only for autoimmune diseases but also for oncological uses – this creates a bit of an analytical conundrum. Since ICER has written about indication specific pricing in the past,^{xx} we wonder why the draft report does not explore that aspect of pricing, cost and affordability. **»We would appreciate ICER discussing this issue.»**

The draft report includes many assumptions that feed into the calculations and modeling. This is not a new phenomenon within ICER evaluations, but we raise it as a problematic issue because it means that the very broad range of confidence for the draft report's quantitative conclusions is not clearly communicated, except in more technical terms, such as in this quote from the draft report: "...imputation in many instances, which affects the level of confidence in the results no matter how responsibly it is done. In addition, key outcome measures such as disease activity scores, remission criteria, and modified Sharp score have undergone substantial revision and modification over the years, are employed variably in clinical trials, and not measured in others, making cross-trial comparisons problematic."^{xxi}

Additional Points

• While we appreciate efforts in the draft report to describe the coverage policies of different health plans for the treatments of interest, given the evolving nature of health insurance

options in the U.S. – particularly for people purchasing their own insurance – we think it would be appropriate for the draft report's "Coverage Policies" section to include information about how the treatments of interest are covered by various short-term/limited duration health plans, Association Health Plans, and Health care sharing ministry coverage^{xxii} options. While we realize that some of those options may not include coverage or reimbursement for any prescription medicines – and may have very high deductibles or annual out-of-pocket limits – we believe that including them in ICER's discussion of coverage policies (even if to just note that the treatments would not be covered by various plans), would provide a more robust and complete picture for U.S. patients, clinicians and policy makers. **» Therefore, we would like ICER to discuss how they might include such information in their coverage section. If such information will not be included, we ask ICER to explain why it will not do so. »**

- The draft report uses the term "compliance" in one instance,^{xxiii} but we believe that "adherence" is a better word choice, which is used elsewhere in the draft report, since it reflects the shared decision making and team approach people with complex chronic conditions should have with their clinicians, whereas "compliance" has much more paternalistic overtones.
- We believe there is a typo in this sentence that contains a triple negative: "Additionally, we do not include a prevalent population of TIM users because we believe it is unlikely that these patients will not switch to upadacitinib...." and suggest that perhaps the final phrase should be "unlikely that these patients <u>will</u> switch to upadacitinib."

Conclusions

Patients Rising Now is very excited that people with rheumatoid arthritis have access to new treatment options. However, we are concerned that access may be limited or barred by insurance plans and their agents through formulary design, cost-sharing structures, of prior authorization requirements. We certainly hope that ICER's actions will not encourage such access restrictions or lead to administrative barriers for clinicians, since any of those outcomes would ultimately harm patients and increase costs for patients, employers and society.

We also believe that people's perspectives are synonymous with societal perspectives, which is why robust and comprehensive analyses of treatment options must include people's viewpoints and concerns. That is why such analyses will only be truly comprehensive if they embrace broad societal perspective including patients' direct out-of-pocket costs <u>and</u> indirect costs related to patients' ability to work, etc. Any analysis that is designed to ethically support society's best interests needs to encompass real patients' choices and goals, the spectrum of financial implications for new therapies, and practical options for increasing value for patients within the pluralistic U.S. health care system. To put it another way: we believe the voices of people with serious health conditions must be a part of defining and assessing the value of treatment options.

Sincerely,

Tenny M. Wilcon

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

xiii Draft report p. 10

^{xv} Draft report p. 56

^{xviii} Draft report p. 9

^{xxi} Draft report p. 34

xxiii Draft report p. 52

ⁱ Draft report p. 1

ⁱⁱ Draft report p. 42

ⁱⁱⁱ Draft report p. 2

^{iv} Draft report p. 5

^v Draft report p. 19

^{vi} Draft report pp. 37-38

vii Draft report pp 16-17

viii FDA label for infliximab, <u>https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103772s5359lbl.pdf</u>
ix <u>https://endpts.com/where-are-the-interchangeable-biosimilars/</u>

^x Draft report p. 19

xi "Indication-specific Pricing of Pharmaceuticals in The U.S. Health Care System: A Report from the 2015 ICER Membership Policy Summit," <u>https://icer-review.org/announcements/isp-white-paper/</u>

^{xii} Draft Report, Figure 1-2, p. 11

xiv Draft report p. 30

^{xvi} Draft Report p. 9

^{xvii} Boytsov N, et al., "Impact of Plan-Level Access Restrictions on Effectiveness of Biologics Among Patients with Rheumatoid or Psoriatic Arthritis," *PharmacoEconomics*. 2019

xix The California Technology Assessment Forum (CTAF), https://icer-review.org/programs/ctaf/

^{** &}quot;Indication-specific Pricing of Pharmaceuticals in The U.S. Health Care System: A Report from the 2015 ICER Membership Policy Summit," <u>https://icer-review.org/announcements/isp-white-paper/</u>

^{xxii} <u>https://www.commonwealthfund.org/publications/fund-reports/2018/aug/health-care-sharing-ministries</u>

IVI * INNOVATION AND VALUE INITIATIVE

November 8, 2019

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

RE: Draft Evidence Report on Janus Kinase Inhibitors for Rheumatoid Arthritis

Dear Dr. Pearson:

The Innovation and Value Initiative (IVI) appreciates the opportunity to offer comments on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on Janus Kinase (JAK) Inhibitors for Rheumatoid Arthritis.

IVI is a 501(c)3 non-profit research organization whose mission is to advance the science and improve the practice of value assessment in healthcare by adapting a more collaborative, open, and tailored approach to examining value, exploring new methods and building models that can support flexible decision making.

As noted in the Draft Evidence Report, IVI previously released an open-source health economic simulation model for assessing the value of RA treatment sequences (the IVI-RA model) as part of IVI's Open-Source Value Project (OSVP). The IVI-RA model was developed and released after the publication of the original ICER review of RA therapies,¹ so we at IVI were encouraged that ICER chose to perform an additional assessment of RA therapies, i.e. JAK inhibitors, and eager to learn about ICER's approach and findings.

Based on our review, we would like to provide the following comments, which encompass feedback on ICER's approach more broadly – specifically, the relevance of the analysis to decision making and the need for transparency – as well as more specific technical comments on the current model, analysis, and report.

Current approach to value assessment does not address the most relevant question

Before addressing details of the current report, we feel that it is important to highlight a fundamental question about the relevance of the current approach to value assessment in the context of a chronic disease.

The Draft Evidence Report provides information on the cost-effectiveness of different JAKs relative to adalimumab as the initial treatment of RA patients who have failed on conventional disease-modifying antirheumatic drugs (DMARDs). Does this information support better

¹ Institute for Clinical and Economic Review (2017). Targeted immune modulators for rheumatoid arthritis: Effectiveness & value. Evidence Report. Accessed November 8, 2019, at: <u>https://icer-review.org/wp-content/uploads/2016/08/NE_CEPAC_RA_Evidence_Report_FINAL_040717.pdf</u>



decisions around treatment selection that will generate the most overall value for patients, insurers, or society overall?

IVI is of the opinion that to be relevant to decision making, value assessment should help to identify how the available treatment options for a given disease can be used in the most cost-effective manner given diversity in the patient population.

In a chronic illness such as RA, patients are generally treated over a period of many years, during which they are likely to cycle through available treatment options as therapies' effectiveness diminishes. In this context, determining whether a specific intervention is cost-effective as a first line therapy for the average patient who failed a conventional DMARD is helpful, but does not address what is arguably the more relevant question: *Given the availability of JAKs, what is the sequence of targeted therapies that provides the most value?*

Developing models to address this question is admittedly more difficult than the approach taken in ICER's analysis and preferably includes evidence regarding the impact of treatment history on efficacy. Models developed through IVI's OSVP, such as the IVI-RA model, provide a starting point for such analyses by allowing flexible individual patient-level simulation of treatment sequences, with flexibility to account for heterogeneity in patient characteristics and outcomes. Rather than falling back on the narrower approach exhibited in the current analysis, we encourage ICER to work with organizations having access to the required evidence and necessary expertise to provide more meaningful and relevant information for decision makers – and ultimately, increase value for both patients and insurers.

ICER's model and analysis should be fully transparent

Given the lack of consensus about the appropriate framework, modeling approaches, and relevant evidence among different stakeholders (i.e. patients, insurers, and providers), IVI strongly believes that all value assessment should occur in a transparent, open-source environment.^{2,3,4} We strongly recommend that ICER provide complete public access to models, underlying data, and other materials. By taking this step, ICER would make important progress toward allaying stakeholder concerns and engaging in a constructive discussion about methods.

Notably, ICER has increased the ease with which models can be made open-source by developing the model for JAKs in RA using hero3, which is based on the open-source R programming language also used to develop IVI's OSVP models. Developing models in R allows for important peer review, validation, and feedback through open-source platforms like GitHub. We are encouraged by ICER's initial movement toward modeling in R and hopeful that it signals movement toward full transparency in modeling and analysis.

² Hay JW. Now Is the Time for Transparency in Value-Based Healthcare Decision Modeling. *Value in Health.* 2019;22(5):564-569.

³ Incerti D, Curtis JR, Shafrin J, Lakdawalla DN, Jansen JP. A Flexible Open-Source Decision Model for Value Assessment of Biologic Treatment for Rheumatoid Arthritis. *Pharmacoeconomics*. 2019 Jun;37(6):829-843.

⁴ Jansen JP, Incerti D, Linthicum MT. Developing Open-Source Models for the US Health System: Practical Experiences and Challenges to Date with the Open-Source Value Project. *Pharmacoeconomics*. 2019 Aug 7.



The implications of modeling assumptions should be made more clear

For the current report on JAKs in RA, ICER chose to use a different model structure from that used in its 2017 evaluation of RA therapies. Although ICER provides a rationale for this decision, it raises the question: what would the results of the cost-effectiveness analysis have been if their previous model would have been used?

This brings us to the topic of structural uncertainty. A recent analysis with the IVI-RA model illustrated the sensitivity of cost-effectiveness estimates to structural modeling assumptions.⁵

In the current model, ICER adopted a 6-month EULAR-to-HAQ mapping algorithm for the 3month DAS28 disease activity categories, assuming remission to reflect "Good" EULAR response, low disease activity to reflect "Moderate" EULAR response, and moderate disease activity and high disease activity to reflect EULAR response of "None." This raises a question about the impact of this assumption on model estimates.

It is important to note that the model structure ICER opted for limits the comparisons that are feasible. If, for example, ACR response categories would have been used to reflect 3 months response with induction treatment then tofacitinib, upadacitinib, and adalimumab could have been compared simultaneously. ACR response categories can be translated into DAS28 response categories given the baseline DAS score, as illustrated with the IVI-RA model.

With ICER's model structure informed by the criterion that it needs to reflect routine practice decision-making, i.e. a 3-month induction response evaluation, one may wonder whether DAS28 is most appropriate. The CDAI score is more practical than DAS-28 in routine assessment of disease activity in RA patients.

In developing the current model, ICER closely reviewed the IVI-RA model and attempted to replicate numerous aspects of it, but chose not to adapt the IVI-RA model with updated evidence on JAKs. In addition to providing necessary transparency by using IVI's open-source model, adaptation of the IVI-RA model would have allowed thorough and efficient evaluation of the implications of structural uncertainty.

Technical comments

In addition to the comments above, we would like to provide several specific comments:

• It is unclear whether the reported response rates with the second line market basket of TIMs in Table 4.5 and Table 4.6 already includes the 16% reduction (i.e. the 0.84 multiplier) or not. In other words, is the 22%, 14%, and 64% used in the model directly or are these estimates adjusted first? In general, the calculation of the treatment

⁵ Linthicum MT. The Impact of Structural Uncertainty on Cost-Effectiveness Estimates. Value Blueprints Research Brief Series. September 3, 2019. Available at: <u>https://www.thevalueinitiative.org/wp-content/uploads/2019/09/2019-09-03.Value-Blueprint_Structural-Uncertainty_FINAL.pdf</u>



responses with the second line market basket is unclear. We would welcome detailed information about the source information and calculations of the estimates provided.

- There seems to be an error in Table 4.18. The difference in total costs between upadacitinib and adalimumab according to the table equals 124,000 97,900 = 26,100, which is not in line with an incremental cost per QALY of 92,000 when the difference in QALYs is 0.699 0.693 = 0.006.
- The representation of the sensitivity analyses is not informative. Figure 4.3, Figure 4.4, Table E7, and Table E8 seem to reflect the sensitivity of the QALYs and costs with upadacitinib at 1-year follow-up rather than the incremental QALYs and costs with upadacitinib versus adalimumab. In addition, one would expect a tornado diagram or table for a measure of cost-effectiveness, such as the incremental net-monetary benefit at a certain willingness-to-pay.

We appreciate the opportunity to provide feedback on the Draft Evidence Report and analysis of JAKs for treatment of RA. We also invite and encourage ICER to seek opportunities to collaborate with organizations such as IVI that are working to improve methods in value assessment.

Sincerely,

Jean for L. Bright

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