February 17, 2017

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

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

Dear Dr. Pearson,

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

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

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

**Executive Summary.** While we understand the current report is not final, the Arthritis Foundation believes we were unable to make comments on the entirety of the document due to the absence of an executive summary. We urge ICER to present a draft executive summary in

future reviews so stakeholders can understand how conclusions will be presented and provide additional comments that could inform the interpretation of the results.

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

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

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

periods of time, and stand to realize fewer QALYs. Table c17, for example, reports only one study included in which mean disease duration was less than 2 years.

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

Without an analysis to address representativeness of the target population, the ICER report must be considered limited as an academic contribution. This is, however, not only an academic publication, but rather a powerful driver of policy. In this draft version, an inattention to representativeness makes this document wholly inappropriate for consideration as a primary influencer of health policy. We urge ICER to better represent the target population by including younger patients and those diagnosed with early/mild RA as part of the target population. Further, we request that an analysis of a broader target group be provided in the main analysis. If inconclusive, we feel strongly that any results obtained in the narrower age group be accompanied by sensitivity analyses that focus on base case age, time since initial diagnosis, base case QALYs, treatment efficacy, and pricing on cDMARD alone or after cDMARD failure. With regard to data presented in Table 15, the report of QALYs attributable to TIMs or cDMARDs does not express the variability of the efficacy of either group. We have concerns regarding DMARD failure where TIMS generally doubled American College of Rheumatology response criteria (ACR20/50/70) effectiveness (e.g., SATORI trial). We thus request that sensitivity tests be included to test values along the variances reported in the studies. The Arthritis Foundation continues to have concerns regarding the citation of Rhor (2016). This paper includes a disclosure that it and its authors were financially sponsored by a company that would stand to benefit from the claims ICER has used this paper to support. We further ask that if these claims cannot be supported by additional studies, that the potential conflict of interest be acknowledged in the ICER report.

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

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

**Other Benefits or Disadvantages.** In regard to the QALY measures used, there is a strong argument that QALYs measured on short-term (often reversible) symptoms do not adequately predict QALYs on longer (2+year) studies. In longer studies irreversible structural damage can be factored into the calculation, and has greater bearing on Health Assessment Questionnaire Disability Index (HAQ-DI). We believe this is a fundamentally important concept as it differentiates symptoms like pain and swelling (measureable in near terms), from functionally compromised joints (which require longer surveillance). We urge ICER to run an analysis of QALYs determined in studies lasting greater than >2 years to see if QALYs associated with any intervention differ from estimates favoring shorter studies. In doing so, ICER may find QALY outcomes beneath the $150,000 threshold of acceptability. Given the differences between the measured QALY and patient sentiment as to the value of these medications, more work to understand this difference of opinion is warranted. As ICER continues to refine this section of their modeling, we ask that ICER recognize that no single QALY threshold estimate can or should be generalizable to all populations, and that QALY thresholds vary by decision-maker, population, and disease. We also ask that ICER expand on their QALY methodology and acknowledge the degree to which uncertainty is present in their conclusions.

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

**Long-Term Cost-Effectiveness.** As previously stated, we believe a glaring issue in the long term cost effectiveness section is the misrepresentation of patients who fail all TIMs and stay

with cDMARD, or no drug therapy for the rest of their lives. The current model assumes that people do not get worse over time without effective treatment, contrary to research. We also remain concerned that patients older or younger than the inclusion criteria are not adequately represented. There is ample evidence to suggest treatment differences and differences in the overall patient experience. Additionally, due to the nature of their insurance, these patients may also differ from those included in the report. We hope that ICER will consider these factors in the final report and subsequent reports on other disease states.

Overall, keeping patients stable on the right medication is critical to maintaining positive health outcomes and greater productivity for patients. We worry that there are parts of ICER's modeling that could threaten a medically stable patient or limit treatment options for patients. The Arthritis Foundation fights to ensure people with arthritis have timely access to the medications they need to function in daily life. We believe attempting to make decisions about the value of a drug without broad-based robust supporting data from patients and providers who are in daily contact with patients is a questionable practice. We ask that the report make mention of the importance of the patient and prescriber relationship in choosing the appropriate treatment for RA patients. We also ask that ICER consider its current process to evaluate and make decisions regarding new treatments. As new treatments and additional information about these treatments become available, we urge ICER to consider publishing a protocol for how these reports will be revised in the future. Further, we ask that ICER develop a patient friendly summary of the reports at the end of each review. Summaries should be concise and easily understood by a patient; we welcome the opportunity to work with ICER on creating a patient-friendly tool.

Finally, the Arthritis Foundation cannot support any recommendations that limit patient access to needed therapies or could result in a patient on a stable drug no longer having access to that drug. We remain confident that ICER will continue to engage and consider the perspective of patients, caregivers, and other stakeholders to ensure that their evidence reports have the broadest possible relevancy. Again, thank you for the opportunity to comment on the *Targeted Immune Modulators for Rheumatoid Arthritis: Effectiveness & Value Draft Evidence Report.* Please contact Sandie Preiss, Arthritis Foundation National Vice President of Advocacy and Access, at 202-887-2910 or spreiss@arthritis.org with questions or for more information.

Sincerely,

Sandie P. Preiss

Sandie Preiss
Vice President, Advocacy and Access
Arthritis Foundation

[i] Ryan, C., Korman, N. J., Gelfand, J. M., Lim, H. W., Elmets, C. A., Feldman, S. R., ... & Van Voorhees, A. S. (2014). Research gaps in psoriasis: opportunities for future studies. *Journal of the American Academy of Dermatology*, *70*(1), 146-167.
[ii] Yazici, Y., Shi, N., & John, A. (2008). Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy.*Bulletin of the NYU hospital for joint diseases*, *66*(2), 77-77.
[iii] Ibid.
[iv] Felson, D. T., & LaValley, M. P. (2014). The ACR20 and defining a threshold for response in rheumatic diseases: too much of a good thing. Arthritis Research & Therapy, 16(1), 101. http://doi.org/10.1186/ar4428
[v] Centers for disease control and prevention. (2015). *Comorbidities*. http://www.cdc.gov/arthritis/data_statistics/comorbidities.htm.
[vi] Faith Matcham, Lauren Rayner, Sophia Steer, Matthew Hotopf; The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology (Oxford) 2013; 52 (12): 2136-2148. doi: 10.1093/rheumatology/ket169
[vii] Arthritis Foundation. (2016). In *Rheumatoid Arthritis and Depression*. http://www.arthritis.org/living-with-arthritis/comorbidities/depression-and-arthritis/depression-rheumatoid-arthritis.php