November 8, 2019

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

PIPC Submits

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 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 decision-making 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 Rheumatoid Arthritis Support Network. RA Facts. Accessed October 22, 2019.

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Rheumatism (EULAR) states, “Treatment decisions should be determined by patient-specific 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.”


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

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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 generally\(^10\) 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.\(^13\)

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


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 meta-analyses 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.

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15 [https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence](https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence)


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,

Tony Coelho

Chairman, Partnership to Improve Patient Care