

## **Disease-Modifying Anti-Rheumatic Drugs for Rheumatoid Arthritis: Effectiveness and Value**

*Draft Background and Scope*  
August 1, 2016

### **Stakeholder Input:**

This scoping document was developed with extensive and critically important input from several patient advocacy organizations. These groups indicated that outcomes, treatment approach, and the overall patient experience differed substantially between rheumatoid arthritis and psoriatic arthritis; as such, ICER has decided to focus attention on rheumatoid arthritis alone for this review and consider psoriatic arthritis as a potential future topic. ICER also engaged with and received input from relevant specialty societies, practicing rheumatologists, and payers to inform the research direction outlined in this draft scope. Input will also be solicited directly from manufacturers during the 3-week public comment period. ICER looks forward to continued engagement with these stakeholders throughout the entire project timeline, up to and including the public meeting in January. We have summarized many of the key inputs to the scoping document in the following paragraph.

Patients and advocacy organizations suggested broad consideration of the available disease-modifying agents, as response to each of these agents can vary substantially according to the patient's disease trajectory, medication history, comorbidities, and other factors. These groups also highlighted the often advanced nature of disease at diagnosis for many patients with rheumatoid arthritis, as the diagnostic process is less than straightforward and can be compounded by limited access to rheumatologists. Some of the challenges inherent in applying clinical trial measures to real-world experience were also discussed, including juxtaposing the binary thresholds for functional improvement used in trials against a more nuanced, "grading curve" assessment of drug performance in clinical practice; and consideration of patient-reported outcomes that may not be common in older trials.

### **Background:**

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, affecting approximately 1.5 million Americans.<sup>1</sup> RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years.<sup>2</sup> RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs) may be involved.<sup>2</sup> RA is considered a clinical syndrome that encompasses several disease subsets, each of which involves a distinct inflammatory cascade that can lead to joint damage, deformity, and organ dysfunction.<sup>3</sup> The course of RA may be complicated by cardiac, hematologic, and other extra-articular manifestations.<sup>2</sup> Historically, RA was associated with both progressive disability and a shortened lifespan, although improvements in diagnosis as well as aggressive use of both non-biologic and biologic disease-modifying anti-rheumatic drugs (DMARDs) have greatly improved prognosis in the past 20 years.<sup>4</sup>

The chemotherapeutic agent methotrexate is the most widely used conventional, non-biologic DMARD; it is considered an "anchor drug" because of its effectiveness and tolerability as well as its potential to enhance the

effectiveness of biologic agents.<sup>2</sup> However, only about 50% of patients treated with methotrexate alone will receive sufficient reduction in disease activity or remission of symptoms. Over the past 18 years, biologic agents designed to interfere with the inflammation characteristic of RA have provided further advances. Agents with indications for RA include inhibitors or antagonists of multiple mediators of the inflammatory cascade, including tumor necrosis factor (TNF), the B-lymphocyte CD20 antigen, interleukin (IL) 1 and 6, Janus kinase (JAK) 1 and 2, and T cells. Novel agents with anti-IL-6 and JAK 1/2 activity are also currently under regulatory review for an RA indication. Guidelines from the American College of Rheumatology recommend use of biologic agents in patients with moderate-to-severe disease activity despite use of conventional DMARDs.<sup>5</sup> Uncertainty remains, however, regarding the relative effectiveness of the different types of biologic agents as well as the appropriate sequence of initial and subsequent biologic therapy. In addition, there are long-term safety concerns with chronic use of biologics in RA that may differ by dose and type of agent.<sup>6</sup> Feedback from patient groups also emphasized the highly individual experience with biologic therapy; some patients see immediate benefit from the first biologic they receive after failure of conventional DMARDs, while others must make multiple attempts before finding an agent that works for them. There is therefore a need to seek evidence on patient subgroups, comorbidities, and other factors that can better inform treatment response and selection of appropriate medications.

### **Report Aim:**

This project will evaluate the health and economic outcomes of multiple biologic agents for moderate-to-severe rheumatoid arthritis. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

### **Scope of the Assessment:**

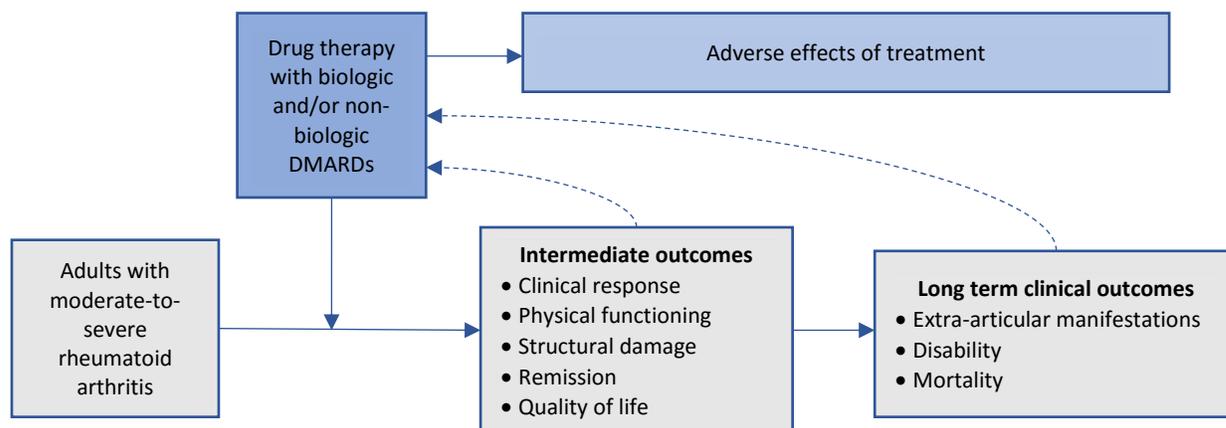
The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be culled from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see <https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/>).

Wherever possible, we will seek out head-to-head studies of these interventions (see page 4 for a detailed list of the agents of interest). We will also include studies with an active comparison to conventional DMARDs as well as placebo-controlled studies. We will consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes.

### **Analytic Framework:**

The general analytic framework for assessment of biologic agents for moderate-to-severe RA is depicted in Figure 1 on the following page.

**Figure 1. Analytic Framework: Disease-Modifying Anti-Rheumatic Drugs for Moderate-to-Severe Rheumatoid Arthritis**



DMARDs: disease-modifying anti-rheumatic drugs

### **Populations**

The population of focus for the review will be adults ages 18 and older with moderate-to-severe rheumatoid arthritis. Note that this focus will not include children, adolescents or adults with juvenile forms of RA or other inflammatory arthritis, now collectively known as juvenile idiopathic arthritis (JIA). Feedback from patient groups and clinicians suggested that the clinical presentation and disease trajectory of these patients differs substantially from those with the adult form of RA.<sup>7</sup>

We will also seek evidence on key subpopulations of interest. Among those suggested by stakeholders during the open input period were: (a) biologic-naïve patients with inadequate response or intolerance to conventional DMARDs versus patients with inadequate response or intolerance to TNF inhibitors or other initial biologic therapy; (b) biologic monotherapy versus combination therapy with conventional DMARDs; (c) route of administration (i.e., oral vs. self-injected vs. infused); and (d) setting of care (e.g., hospital-based vs. ambulatory infusion centers).

### **Interventions**

Clinical experts and patient organizations advised us that it is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate. We also received input that fail-first insurance policies often require patients to follow a specific sequence of biologic therapies, yet it is unclear whether established protocols are based on the most current clinical evidence. For these reasons we will consider a comprehensive list of biologic DMARDs with FDA indications for RA as well as two investigational therapies presently undergoing FDA review. Interventions of interest are listed by class below.

- TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
- CD20-directed cytolytic antibody (rituximab)
- T-cell inhibitor (abatacept)
- IL-1 inhibitor (anakinra)
- IL-6 inhibitors (tocilizumab, sarilumab [investigational])
- JAK1/2 inhibitors (tofacitinib, baricitinib [investigational])

We will seek clinical evidence on all forms of the products listed above, including biosimilar forms as data permit.

### **Comparators**

We expect that most available clinical trials of biologics will have been conducted in patients without adequate response to initial therapy with conventional DMARDs (e.g., methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), yet will involve comparisons to conventional agents nonetheless for purposes of regulatory approval. We will examine studies comparing biologic agents to conventional DMARD monotherapy or combination therapy to assess performance versus historical standard treatment, but will also seek head-to-head studies between biologic therapies to evaluate for more contemporary comparisons. Comparisons of biologic agents will be conducted among drugs with similar mechanisms of action (e.g., all TNF inhibitors) as well as between drugs with different mechanisms (e.g., IL-6 inhibitors vs. JAK 1/2 inhibitors).

Finally, while studies with an active comparator arm are preferred, we will also include placebo-controlled trials as necessary to complete a planned network meta-analysis of the effects of treatment on key measures of effectiveness that will combine direct and indirect evidence.

### **Outcomes**

This review will examine key clinical outcomes associated with RA. In conversations held to develop the draft scoping document, patient organizations advised us that clinical trials are often lacking robust information on patient-reported outcomes, and suggested a focus on recently-developed measures such as those described in the federally-funded PROMIS toolkit (<http://www.healthmeasures.net/explore-measurement-systems/promis>). We will also explore key clinical and health utilization outcomes as listed below.

Outcomes of interest include:

- Mortality
- Treatment response (e.g., ACR20, ACR50, and ACR70, area-under-the-curve analysis)
- Disease activity (e.g., DAS28, CDAI)
- Remission (e.g., PAS or PASII, RAPID-3, ACR Core Data Set)
- Radiographic evidence of structural damage
- Key laboratory-based indices (e.g., erythrocyte sedimentation rate, C-reactive protein)
- Disease-specific and general health-related quality of life (e.g., HAQ-DI, SF-36)
- Other patient-reported outcomes (as available)
- Development of neutralizing antibodies
- Treatment-related adverse events (e.g., serious infection, malignancy, liver abnormalities)
- Costs and cost-effectiveness of biologic treatments

While we will seek to assess these outcomes quantitatively, some measures may not be widely reported and will necessitate descriptive analysis only. Where possible we will report the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

Stakeholders also recommended that we seek evidence describing the impact of dose levels and dose changes on the outcomes of interest. Specifically, we will assess the impact of dose increases, dose decreases, and drug cessation during periods of sustained control or remission on long-term outcomes, as well as the effects of dose levels on the rates of serious adverse events.

### **Timing**

Evidence on intervention effectiveness will be derived from studies of at least six months' duration, while information on potential harms will be obtained from studies of at least three months' duration.

## **Settings**

All relevant settings will be considered, including outpatient as well as ambulatory and hospital-based infusion centers.

### **Simulation Models Focusing on Comparative Value:**

Biologic agents for moderate-to-severe RA are expensive, and there is evidence that both their prices and the proportion of those costs paid by patients have increased substantially in recent years.<sup>8</sup> As a complement to the evidence review, we will develop a microsimulation model to assess the cost-effectiveness of each of the biologic agents listed earlier relative to conventional DMARDs and/or alternative biologic agents. The model framework and inputs will be based on previous models that evaluated biologic therapies for RA management.<sup>9-12</sup> The target population will consist of adult patients with moderate-to-severe RA who have an inadequate response to prior therapy. Alternative strategies will be evaluated, including (a) use of biologic agents in biologic-naïve patients with an inadequate response to conventional DMARDs; and (b) use of a second biologic agent in patients with an inadequate response to initial biologic therapy. Based on feedback from clinical experts and patient groups, TNF inhibitors will be considered the initial biologic for scenario (b). A lifetime time horizon will be used to reflect the chronic nature of RA. The economic evaluation will be from a health-system perspective, and will thus largely focus on direct medical costs.

The sequential treatment microsimulation model will model a hypothetical homogenous cohort of patients, with baseline characteristics similar to the populations of the randomized controlled trials identified in the evidence review, from the initiation of a biologic until death. After starting a biologic, the model will simulate the American College of Rheumatology (ACR) response and the Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index (HAQ-DI) after six months. Patients who withdraw from a biologic DMARD may switch to another biologic with a similar mechanism of action, switch to a biologic with a different mechanism of action, or return to the use of conventional DMARDs. A cycle length of six months will be used to reflect the time need to conclude a treatment's efficacy.<sup>10</sup> The ACR response will be mapped with an increase in HAQ-DI score using statistical models previously developed by Wailoo and colleagues.<sup>9</sup> The HAQ-DI score will then be linked to utility and cost. The model will continue to simulate the long-term HAQ-DI score every six months until withdrawal from the treatment or death.

Key model inputs will include the distribution of ACR response (e.g., percent of patients achieving a less than 20% improvement, a 20-49% improvement, a 50% or greater improvement, etc.), quality of life values, and costs associated with drug therapy, physician visits, and hospitalizations. ACR response probabilities will differ between interventions to reflect the differences in effectiveness. Treatment effectiveness will be estimated using evidence from published randomized controlled trials identified in the evidence review.

The health outcome of each intervention will be evaluated in terms of responses achieved, life-years, and quality-adjusted life years (QALYs). Relevant pairwise comparisons will be made between treatment pathways, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per response or remission achieved. We will conduct a separate analysis to attempt to extend the perspective to a societal one in order to include the indirect costs due to productivity losses. Given available evidence, further scenario analyses will address biologic DMARD price changes over time as well as biosimilar introduction.

In an additional analysis, we will also explore the potential health system budgetary impact of each treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. These budgetary impact analyses will assume specific "uptake" rates for new products over a five-year period in the populations of interest, and will utilize available market share data for existing products to measure budgetary impact. This analysis will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating product uptake and calculating potential budget impacts can be found at: <http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf>.

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