**National Quality Forum—Evidence (subcriterion 1a)**

**Measure Number** (*if previously endorsed*)**:** Click here to enter NQF number

**Measure Title**: Rheumatoid Arthritis: Disease Modifying Anti-Rheumatic Drug (DMARD) Therapy

**IF the measure is a component in a composite performance measure, provide the title of the Composite Measure here:** Click here to enter composite measure #/ title

**Date of Submission**: 2/14/2014

|  |
| --- |
| **Instructions**  *For composite performance measures:*  *A separate evidence form is required for each component measure unless several components were studied together.*  *If a component measure is submitted as an individual performance measure, attach the evidence form to the individual measure submission.*   * Respond to all questions as instructed with answers immediately following the question. All information needed to demonstrate meeting the evidence subcriterion (1a) must be in this form. An appendix of *supplemental* materials may be submitted, but there is no guarantee it will be reviewed. * If you are unable to check a box, please highlight or shade the box for your response. * Maximum of 10 pages (*incudes questions/instructions*; minimum font size 11 pt; do not change margins). ***Contact NQF staff if more pages are needed.*** * Contact NQF staff regarding questions. Check for resources at [Submitting Standards webpage](http://www.qualityforum.org/Measuring_Performance/Submitting_Standards.aspx). |

|  |
| --- |
| **Note: The information provided in this form is intended to aid the Steering Committee and other stakeholders in understanding to what degree the evidence for this measure meets NQF’s evaluation criteria.**   1a. Evidence to Support the Measure Focus The measure focus is evidence-based, demonstrated as follows:   * Health outcome: [**3**](#Note3) a rationale supports the relationship of the health outcome to processes or structures of care. Applies to patient-reported outcomes (PRO), including health-related quality of life/functional status, symptom/symptom burden, experience with care, health-related behavior. * Intermediate clinical outcome: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4)that the measured intermediate clinical outcome leads to a desired health outcome. * Process: [**5**](#Note5) a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured process leads to a desired health outcome. * Structure: a systematic assessment and grading of the quantity, quality, and consistency of the body of evidence [**4**](#Note4) that the measured structure leads to a desired health outcome. * Efficiency: [**6**](#Note6) evidence not required for the resource use component.   **Notes**  **3.** Generally, rare event outcomes do not provide adequate information for improvement or discrimination; however, serious reportable events that are compared to zero are appropriate outcomes for public reporting and quality improvement.  **4.** The preferred systems for grading the evidence are the U.S. Preventive Services Task Force (USPSTF) [grading definitions](http://www.uspreventiveservicestaskforce.org/uspstf/grades.htm) and [methods](http://www.uspreventiveservicestaskforce.org/methods.htm), or Grading of Recommendations, Assessment, Development and Evaluation [(GRADE) guidelines](http://www.gradeworkinggroup.org/publications/index.htm).  **5.** Clinical care processes typically include multiple steps: assess → identify problem/potential problem → choose/plan intervention (with patient input) → provide intervention → evaluate impact on health status. If the measure focus is one step in such a multistep process, the step with the strongest evidence for the link to the desired outcome should be selected as the focus of measurement. Note: A measure focused only on collecting PROM data is not a PRO-PM.  **6.** Measures of efficiency combine the concepts of resource use and quality (see NQF’s [Measurement Framework: Evaluating Efficiency Across Episodes of Care](http://www.qualityforum.org/Publications/2010/01/Measurement_Framework__Evaluating_Efficiency_Across_Patient-Focused_Episodes_of_Care.aspx); [AQA Principles of Efficiency Measures](http://www.aqaalliance.org/files/PrinciplesofEfficiencyMeasurementApril2006.doc)). |

**1a.1.This is a measure of**: (*should be consistent with type of measure entered in De.1*)

Health outcome: Click here to name the health outcome

Patient-reported outcome (PRO): Click here to name the PRO

*PROs include HRQoL/functional status, symptom/symptom burden, experience with care, health-related behaviors*

Intermediate clinical outcome (*e.g., lab value*): Click here to name the intermediate outcome

Process: **Disease modifying anti-rheumatic drug (DMARD) prescription for patients with rheumatoid arthritis**

Structure: Click here to name the structure

Other: Click here to name what is being measured

There is an existing NQF-endorsed measure regarding DMARD use in RA patients is entitled, *“Disease-modifying anti-rheumatic drug therapy for rheumatoid arthritis: percentage of members who were diagnosed with rheumatoid arthritis and who were dispensed at least one ambulatory prescription for a disease modifying anti-rheumatic drug (DMARD)*.”

This application builds e-specifications (construction of an “e-measure”) for the DMARD quality measure and also provides an update on both scientific evidence and performance data on this measure.

This measure is used to assess the percentage of patients who were diagnosed with rheumatoid arthritis and who were dispensed at least one ambulatory prescription for a disease modifying anti-rheumatic drug (DMARD).

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**HEALTH OUTCOME/PRO PERFORMANCE MEASURE**  *If not a health outcome or PRO, skip to* [*1a.3*](#Section1a3)

**1a.2.** **Briefly state or diagram the path between the health outcome (or PRO) and the healthcare structures, processes, interventions, or services that influence it.**

**1a.2.1.** **State the rationale supporting the relationship between the health outcome (or PRO) to at least one healthcare structure, process, intervention, or service (*i.e., influence on outcome/PRO*).**

*Note: For health outcome/PRO performance measures, no further information is required; however, you may provide evidence for any of the structures, processes, interventions, or service identified above.*

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**intermediate outcome, PROCESS, or STRUCTURE PERFORMANCE measure**

**1a.3.****Briefly state or diagram the path between structure, process, intermediate outcome, and health outcomes**. Include all the steps between the measure focus and the health outcome.

DMARD prescription 🡪 DMARD use 🡪 decreased disease activity and erosions 🡪 decreased disability, decreased pain, improved functional status, improved health-related quality of life

Disease modifying anti-rheumatic drugs (DMARDs) improve the disease course of rheumatoid arthritis (RA) through attenuation of progression of bony erosions, reduction of inflammation and long-term structural damage. The utilization of DMARDs also improves functional status in individuals with RA.

RA is a chronic autoimmune disorder often characterized by progressive joint destruction and multisystem involvement. It affects approximately 1.3 million Americans and affects women disproportionately (*Helmick CG et al., Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Am J Public Health. 2012 Mar;102(3):426-33*). There is no cure; consequently, the goal of treatment is to slow the progression of the disease and thereby delay or prevent joint destruction, relieve pain, and maintain functional capacity.

Evidence-based guidelines, summarized below, support early initiation of DMARD therapy in patients diagnosed with RA. All patients with RA are candidates for DMARD therapy, and the majority of newly diagnosed individuals should be started on DMARD therapy within three months of diagnosis.

**1a.3.1.** **What is the source of the systematic review of the body of evidence that supports the performance measure?**

Clinical Practice Guideline recommendation – ***complete sections*** [***1a.4***](#Section1a4)***, and [1a.7](#Section1a7)***

US Preventive Services Task Force Recommendation – ***complete sections*** [***1a.5***](#Section1a5) ***and*** [***1a.7***](#Section1a7)

Other systematic review and grading of the body of evidence (*e.g., Cochrane Collaboration, AHRQ Evidence Practice Center*) – ***complete sections*** [***1a.6***](#Section1a6) ***and [1a.7](#Section1a7)***

Other – ***complete section*** [***1a.8***](#Section1a8)

*Please complete the sections indicated above for the source of evidence. You may skip the sections that do not apply.*

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.4. CLINICAL PRACTICE GUIDELINE RECOMMENDATION**

**1a.4.1.** **Guideline citation** (*including date*) and **URL for guideline** (*if available online*):

Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Mar 2014; 73(3): 492–509. **Level of evidence 1A, Grade A, Strength of recommendation 9.8**.

American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46. Level of Evidence C.

Singh, et al., 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. AC&R 2012;64(5):625-639. Evidence grades are provided in this guideline. Evidence rating for overall DMARD use not performed.

**1a.4.2.** **Identify guideline recommendation number and/or page number** and **quote verbatim, the specific guideline recommendation**.

p. 6 “Therapy with DMARDs should be started as soon as the diagnosis of RA is made” from *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Mar 2014; 73(3): 492–509*.

p. 328 “The majority of patients with newly diagnosed RA should be started on disease-modifying antirheumatic drug (DMARD) therapy within 3 months of diagnosis” from *American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46*.

DMARD use is implicit in the most recent ACR RA guideline; no specific rating for overall DMARD use is therefore provided. “The 2012 revision updates the 2008 ACR recommendations in the following areas: 1) indications for DMARDs and biologic agents, 2) switching between DMARD and biologic therapies…” in *Singh, et al., 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. AC&R 2012;64(5):625-639*.

**1a.4.3.** **Grade assigned to the quoted recommendation with definition of the grade:**

Level of Evidence 1a and Grade A, strength of recommendation 9.8 out of 10 (*Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Mar 2014; 73(3): 492–509*). Levels of evidence and grades of recommendation based on the Oxford Levels of Evidence assessment, as well as the primary voting results of a Task Force meeting and level of agreement/strength of recommendation voting by the Task Force.

Additional evidence ratings provided in *Gaujoux-Viala C et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9* and *Nam JL et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun;69(6):976-86*.

Synthetic DMARD used in DMARD-naïve patient: Level of Evidence 1B

Biologic DMARD used in DMARD-naïve patient: Level of Evidence 2B

Biologic DMARD used in methotrexate-naïve patient (but had prior DMARDs): Level of Evidence 1B

Definitions are provided below:

From the Centre for Evidence-Based Medicine, Oxford

1a: Systematic reviews (with homogeneity) of randomized controlled trials

1b: Individual randomized controlled trials (with narrow confidence interval)

1c: All or none randomized controlled trials

2a: Systematic reviews (with homogeneity) of cohort studies

2b: Individual cohort study or low quality randomized controlled trials (e.g. <80% follow-up)

2c: "Outcomes" Research; ecological studies

3a: Systematic review (with homogeneity) of case-control studies

3b: Individual case-control study

4: Case-series (and poor quality cohort and case-control studies)

5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

|  |  |  |
| --- | --- | --- |
| A | High | Further research is very unlikely to change our confidence in the estimate of effect.  Several high-quality studies with consistent results  In special cases: one large, high-quality multi-centre trial |
| B | Moderate | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. One high-quality study or  Several studies with some limitations |
| C | Low | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  One or more studies with severe limitations |
| D | Very Low | Any estimate of effect is very uncertain.  Expert opinion or No direct research evidence or One or more studies with very severe limitations |

**1a.4.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: If separate grades for the strength of the evidence, report them in section 1a.7.*)

Older American College of Rheumatology evidence ratings (Level C) are not reviewed here since ratings pre-dated the last decade of clinical trials (*American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46*).

**1a.4.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.4.1*)**:**

Detailed information regarding the Oxford evidence rating methodology (which employs the GRADE and Centre for Evidence-Based Medicine, Oxford (1a-5) is also available at: <http://www.essentialevidenceplus.com/product/ebm_loe.cfm>.

Guyatt G et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines. Chest. 2006;129(1):174-181 and <http://www.gradeworkinggroup.org>.

**1a.4.6. If guideline is evidence-based (rather than expert opinion), are the details of the quantity, quality, and consistency of the body of evidence available (e.g., evidence tables)?**

Yes **→ *complete section [1a.7](#Section1a7)***

No **→ *report on another systematic review of the evidence in sections*** [***1a.6***](#Section1a6) ***and*** [***1a.7***](#Section1a7)***; if another review does not exist, provide what is known from the guideline review of evidence in*** [***1a.7***](#Section1a7)

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.5.** **UNITED STATES PREVENTIVE SERVICES TASK FORCE RECOMMENDATION**

**1a.5.1.** **Recommendation citation** (*including date*) and **URL for recommendation** (*if available online*):

**1a.5.2.** **Identify recommendation number and/or page number** and **quote verbatim, the specific recommendation**.

**1a.5.3.** **Grade assigned to the quoted recommendation with definition of the grade**:

**1a.5.4. Provide all other grades and associated definitions for recommendations in the grading system.** (*Note: the* *grading system for the evidence should be reported in section 1a.7.*)

**1a.5.5. Citation and URL for methodology for grading recommendations** (*if different from 1a.5.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.6. OTHER SYSTEMATIC REVIEW OF THE BODY OF EVIDENCE**

**1a.6.1.** **Citation** (*including date*) and **URL** (*if available online*):

**1a.6.2.** **Citation and** **URL for methodology for evidence review and grading** (*if different from 1a.6.1*)**:**

***Complete section*** [***1a.7***](#Section1a7)

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.7. FINDINGS FROM SYSTEMATIC REVIEW OF BODY OF THE EVIDENCE supporting the measure**

*If more than one systematic review of the evidence is identified above, you may choose to summarize the one (or more) for which the best information is available to provide a summary of the quantity, quality, and consistency of the body of evidence. Be sure to identify which review is the basis of the responses in this section and if more than one, provide a separate response for each review.*

The most recent systematic review and evidence ratings on DMARD use in RA are referred to in *Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. Mar 2014; 73(3): 492–509*. Evidence was found to be Level 1a, Grade A, leading to a Strong Recommendation (see definitions above). There is consistent, high-quality evidence that DMARDs modify the disease course in RA, leading to less disease activity, less disease damage, and less disability and pain.

Additional systematic literature reviews have been conducted (most recently, *Gaujoux-Viala C et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9* and *Nam JL et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis. 2010 Jun;69(6):976-86*).

With regard to specific studies mentioned in these reviews, the majority of the evidence comes from studies that either compare the efficacy of a single DMARD (e.g. methotrexate) vs. another agent or combination therapy, or compare DMARDs to placebo. **In sum, the following DMARDs were shown to be superior to placebo:** leflunomide, sulfasalazine, intramuscular gold, hydroxychloroquine, auranofin, cyclosporine, tetracyclins, azathioprine, and tacrolimus (*Gaujoux-Viala et al*, supplemental appendix ). Methotrexate alone or in combination was found to be superior to all other synthetic DMARDs. Biologic DMARDs including abatacept, adalimumab, etanercept, infliximab were found to improve clinical outcomes in methotrexate-naïve patients and among those in whom methotrexate was ineffective (Oxford level of evidence 1B). Methotrexate alone or in combination with a biologic agent were the most effective regimens.

**1a.7.1.** **What was the specific structure, treatment, intervention, service, or intermediate outcome addressed in the evidence review?**

Reviews examined whether drug therapy with DMARD was effective in altering health outcomes, including modifying RA disease activity. Additional studies have examined the impact of DMARD therapy on functional outcomes, pain, disability and health-related quality of life.

**1a.7.2.** **Grade assigned for the quality of the quoted evidence with definition of the grade**:

See evidence ratings and definitions above.

**1a.7.3. Provide all other grades and associated definitions for strength of the evidence in the grading system.**

See definitions provided above.

**1a.7.4.** **What is the time period covered by the body of evidence? (*provide the date range, e.g., 1990-2010*). Date range**:

The literature search included studies from 1962 through February 2009.

**QUANTITY AND QUALITY OF BODY OF EVIDENCE**

**1a.7.5.****How many and what type of study designs are included in the body of evidence**? (*e.g., 3 randomized controlled trials and 1 observational study*)

In the synthetic DMARD review, 97 randomized trials were included. In the biologic DMARD review, 87 articles and 40 abstracts describing randomized trials were included.

**1a.7.6.** **What is the overall quality of evidence across studies in the body of evidence**? (*discuss the certainty or confidence in the estimates of effect particularly in relation to study factors such as design flaws, imprecision due to small numbers, indirectness of studies to the measure focus or target population*)

Only RCTs were included, and the pooled studies had relatively large sample sizes. There is substantial, high quality data supporting this measure.

**ESTIMATES OF BENEFIT AND CONSISTENCY ACROSS STUDIES IN BODY OF EVIDENCE**

**1a.7.7.** **What are the estimates of benefit—magnitude and direction of effect on outcome(s) across studies in the body of evidence**? (*e.g., ranges of percentages or odds ratios for improvement/ decline across studies, results of meta-analysis, and statistical significance*)

In studies comparing synthetic DMARDs to placebo, most drugs conferred an odds ratio of at least 2.0 when looking at the outcome of disease activity (measured by ACR20). In other words, most DMARDs have at least a 2-fold odds improvement in disease activity compared to placebo, and methotrexate and biologic drugs used alone or in combination have even more dramatic effects.

For example, leflunomide was more efficacious than placebo on swollen joint count (4 studies, 987 patients, SRM= 0.50 [0.37, 0.62]) (2-5) (Figure C), on pain (4 studies, 987 patients, SRM= 1.60 [0.41, 2.80]) (2-5), on disability (4 studies, 987 patients, SRM= 0.50 [0.27, 0.72]) (2-5), on ACR 20 response criteria (3 studies, 784 patients, OR= 3.22 [2.36, 4.39]) (3-5), on ACR 50 response criteria (3 studies, 784 patients, OR= 3.88 [2.54, 5.91]) (3-5), on ACR 70 response criteria (2 studies, 563 patients, OR= 5.30 [2.45, 11.47]) (4,5) and on structure (2 studies, 365 patients, SRM= 0.25 [0.04, 0.46]) (3-4) (Table A).

A pooled analysis indicated that methotrexate was more efficacious in reducing signs and symptoms, disability and radiographic structural damage than other synthetic DMARDs pooled: ES for swollen joint count (SJC) versus pooled DMARDs=1.42 (95% CI 0.65 to 2.18).

Biologic DMARDs used alone were found to be equivalent to methotrexate used alone: For example,

12-month ACR20 responses from two studies on adalimumab and etanerecept showed a RR=0.87 (95% CI 0.74 to 1.03) and 1.22 (95% CI 1.06 to 1.4), respectively; overall RR=0.98 (95% CI 0.76 to 1.26)

**1a.7.8.** **What harms were studied and how do they affect the net benefit (benefits over harms)?**

Adverse effects of synthetic and biologic DMARDs were studied during the course of the trials, including infections, liver toxicity, and bone marrow suppression, among others. As a result of the safety signals detected in the trials and in observational studies, the ACR has summarized contraindications and recommendations for monitoring for drug toxicity in their clinical guidelines. The benefits of DMARDs in rheumatoid arthritis are still net positive when drugs are used in the appropriate context.

**UPDATE TO THE SYSTEMATIC REVIEW(S) OF THE BODY OF EVIDENCE**

**1a.7.9.** **If new studies have been conducted since the systematic review of the body of evidence, provide for each new study: 1) citation, 2) description, 3) results, 4) impact on conclusions of systematic review**.

**\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

**1a.8 OTHER SOURCE OF EVIDENCE**

*If source of evidence is NOT from a clinical practice guideline, USPSTF, or systematic review, please describe the evidence on which you are basing the performance measure.*

**1a.8.1** **What process was used to identify the evidence?**

**1a.8.2.** **Provide the citation and summary for each piece of evidence.**