

Developing a Construct to Evaluate Flares in Rheumatoid Arthritis: A  
Conceptual Report of the OMERACT RA Flare Definition Working Group

RIEKE ALTEN, CHRISTOF POHL, ERNEST H. CHOY, ROBIN CHRISTENSEN, DANIEL  
E. FURST, SARAH E. HEWLETT, AMYE LEONG, JAMES E. MAY, TESSA C.  
SANDERSON, VIBEKE STRAND, THASIA G. WOODWORTH, CLIFTON O. BINGHAM III  
and The OMERACT RA Flare Definition Working Group

J Rheumatol 2011;38;1745-1750  
<http://www.jrheum.org/content/38/8/1745>

1. Sign up for TOCs and other alerts  
<http://www.jrheum.org/alerts>
2. Information on Subscriptions  
<http://jrheum.com/faq>
3. Information on permissions/orders of reprints  
[http://jrheum.com/reprints\\_permissions](http://jrheum.com/reprints_permissions)

*The Journal of Rheumatology* is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

# Developing a Construct to Evaluate Flares in Rheumatoid Arthritis: A Conceptual Report of the OMERACT RA Flare Definition Working Group

RIEKE ALTEN, CHRISTOF POHL, ERNEST H. CHOY, ROBIN CHRISTENSEN, DANIEL E. FURST, SARAH E. HEWLETT, AMYE LEONG, JAMES E. MAY, TESSA C. SANDERSON, VIBEKE STRAND, THASIA G. WOODWORTH, CLIFTON O. BINGHAM III, and The OMERACT RA Flare Definition Working Group

**ABSTRACT.** Rheumatoid arthritis (RA) patients and healthcare professionals (HCP) recognize that episodic worsening disease activity, often described as a “flare,” is a common feature of RA that can contribute to impaired function and disability. However, there is no standard definition to enable measurement of its intensity and impact. The conceptual framework of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA Flare Definition Working Group includes an anchoring statement, developed at OMERACT 9 in 2008: “flare in RA” is defined as worsening of signs and symptoms of sufficient intensity and duration to lead to change in therapy. Subsequently, domains characterizing flare have been identified by comprehensive literature review, patient focus groups, and patient/HCP Delphi exercises. This led to a consensus regarding preliminary domains and a research agenda at OMERACT 10 in May 2010. The conceptual framework of flare takes into account validated approaches to measurement in RA: (1) various disease activity indices (e.g., Disease Activity Score, Clinical Disease Activity Index, Simplified Disease Activity Index); (2) use of patient-reported outcomes (PRO); and (3) characterization of minimally clinically detectable and important differences (MCDD, MCID). The measurement of RA flare is composed of data collection assessing a range of unique domains describing key features of RA worsening at the time of patient self-report of flare, and then periodically for the duration of the flare. The components envisioned are: (1) Patient self-report using a “patient global question” with well characterized and validated anchors; (2) Patient assessment using a flare questionnaire and PRO available at the time of each self-report; (3) Physician/HCP assessment of disease activity status; and (4) Physician’s determination whether to change treatment. In randomized controlled trials and observational studies, such a conceptual approach is intended to lead to a valid measure of this outcome/response, thus expanding an understanding of the true impact of a therapy to limit disease activity. Clinically, this approach is intended to enhance patient-HCP communication. This article describes the conceptual framework being used by the OMERACT RA Flare Definition Working Group in developing a standardized method for description and measurement of “flare in RA” to guide individual patient treatment. (J Rheumatol 2011;38:1745-50; doi:10.3899/jrheum.110400)

*Key Indexing Terms:*

RHEUMATOID ARTHRITIS	FLARE	WORSENING	DISEASE ACTIVITY
PATIENT PERSPECTIVE			OUTCOME MEASURES

The term “flare in RA” is commonly used by both patients and clinicians to describe episodes of worsening signs and symptoms, often a temporary state, but sometimes indicating persistent deterioration from a previous state. While periodic

fluctuations of disease activity are common in RA, these vary widely in their intensity, frequency, duration, and impact on the patient. There is no commonly accepted understanding of the constituents of a “flare in RA” or a standardized method

From Schlosspark Klinik, Charité University Medicine, Berlin, Germany; Academic Department of Rheumatology, King's College London, London, UK; The Parker Institute, Musculoskeletal Statistics Unit, Copenhagen University Hospital, Frederiksberg, Denmark; University of California at Los Angeles Medical School, University of the West of England, Bristol, UK; Healthy Motivation, Bone and Joint Decade, Santa Barbara, California, USA; National Fathers' Network, Seattle, Washington, USA; Stanford University, Portola Valley, California, USA; Leading Edge Clinical Research LLC, Stuart, Florida, USA; and Johns Hopkins University, Baltimore, Maryland, USA.

Supported by UCB, Amgen, BMS, Xoma, Roche/Genentech, Centocor, Pfizer, The Arthritis Society, IDENK. The Parker Institute, Musculoskeletal Statistics Unit, is supported by grants from OAK Foundation.

R. Alten, MD; C. Pohl, MD, Schlosspark Klinik, Charité University Medicine; E.H. Choy, MD, FRCP, Academic Department of Rheumatology, King's College London; R. Christensen, MSc, PhD, Parker Institute, Musculoskeletal Statistics Unit, Copenhagen University Hospital; D.E. Furst, MD, UCLA Medical School; S.E. Hewlett, PhD, RN, University of the West of England; A. Leong, President, CEO, Healthy Motivation; Spokesperson, Director of Strategic Relations, Bone and Joint Decade; J.E. May, Educator/Mental Health Consultant, Director, National Fathers' Network (retired); T.C. Sanderson, PhD, MSc, University of the West of England; V. Strand, MD, Stanford University; T.G. Woodworth, MD, Leading Edge Clinical Research LLC; C.O. Bingham III, MD, Johns Hopkins University. Dr. Woodworth and Dr. Bingham share senior authorship.

Address correspondence to Dr. R. Alten; E-mail: rieke.alten@schlosspark-klinik.de

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2011. All rights reserved.

to accurately quantify these events<sup>1</sup>. Patients will often describe “good days” and “bad days,” but may have difficulty communicating the severity and impact of their “bad days” to their healthcare provider (HCP). Clinicians will often require changes in “objective measures,” such as increases in joint swelling and tenderness or worsening in laboratory values such as C-reactive protein (CRP) or/and erythrocyte sedimentation rate (ESR) in making a decision whether a patient is in a flare. These differences in perspectives between patients and clinicians may lead to erroneous assumptions of the actual aggregate state of disease activity and its impact on function and quality of life<sup>2</sup>.

With the advent of more effective therapies, the need to detect, measure, and assess flare becomes more apparent. Thus, validating a definition should enhance clinical research and facilitate clinical decision-making. An accepted definition, for example, could be a study endpoint or guide medication tapering, retreatment, or changed pharmacotherapy or self-management strategies<sup>3,4</sup>.

This article describes the conceptual framework being used by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA Flare Definition Working Group in developing a standardized method for description and measurement of “flare in RA,” initially in the context of randomized controlled trials (RCT) and longitudinal observational studies (LOS), and ultimately to guide individual patient treatment.

### Why Define Flare in RA?

Flares are a common occurrence in patients with RA and likely represent an under-recognized and potentially disabling aspect of the disease experience. There are limited data to inform us on the nature and impact of flares<sup>5,6,7</sup>. Whether these episodes of flare, their intensity, frequency, and/or their duration can be mitigated or modulated has not been studied, in part because we lack a fundamental understanding of many aspects of the experience of RA flare.

With the recognition of flares as an integral feature of disease for most RA patients, there is an opportunity, if not a requirement, to evaluate their impact, and to incorporate an assessment of flares into the design of RCT assessing therapeutic efficacy (Table 1).

At OMERACT 8, a decision was made to develop a standardized definition of flare in RA, recognizing that such a definition was lacking for the reporting of RA flare as an adverse event. In addition, for RCT such a definition appeared to be needed to fully define “Remission” or “Low Disease Activity,” and to characterize a relevant aspect of the benefit versus risk of potent biologic therapies<sup>8,9</sup>. In addition, such a definition is needed to determine ability to taper therapy once remission is established, and to determine an optimally effective maintenance regimen. Potential endpoints include “time to flare” (i.e., duration of benefit), absence of flare, number of flares over a period of time<sup>10</sup>, or time of readministration<sup>11,12,13</sup>, as used for studies in juvenile inflammatory arthritis<sup>14</sup>.

In the absence of an established flare definition, studies to date have largely used an inverse of a response measure developed and validated to measure disease improvement (e.g., increase in Disease Activity Score 28)<sup>15,16,17,18</sup>. The validity of these thresholds as minimally important increases in disease activity, however, has not been established. Finally, an important category requiring definition of “flare in RA” is the assessment of flare as an adverse event, given that absence of disease activity should include the absence of episodic, often unpredictable worsening. Such a definition would be enhanced by additional descriptors to define severity/intensity. As noted above, such a standardized definition could be used in monitoring the efficacy of treatment (e.g., absence of moderate to severe flares), and could provide context to assess self-management [e.g., short-term increases in nonsteroidal antiinflammatory drugs (NSAID) or/and corticosteroids]<sup>1,8</sup>.

### Heterogeneous Signs and Symptoms of Flare

The heterogeneity of signs and symptoms that may constitute a flare is recognized by patients and their clinicians; similarly, there is variation in the specific actions and interventions taken, dependent on a variety of factors such as intensity, frequency, manageability, and duration. Some exacerbations are short-lived (e.g., a “bad day”) and often managed by the patient with watchful waiting or with changes in activities, pacing, rest, or nonpharmacological interventions. Others may be of sufficient severity that patients self-manage with increased analgesics, NSAID, or short-term increase in corticosteroid dose. Finally, there are flares of sufficient intensity that patients request HCP consultation and change in treatment. Although the phenomenology of flare is well recognized by both clinicians and patients, there are no generally agreed-upon parameters to define disease flare/worsening, to characterize its severity, or to describe its onset and duration.

Within the OMERACT RA Flare Definition Working Group, qualitative research with patients, systematic literature reviews<sup>1</sup>, and parallel iterative Delphi processes (healthcare providers and researchers, patient research partners) yielded a preliminary set of unique domains that characterized the flare experience<sup>1,19</sup>. After obtaining final consensus regarding essential domains for detection and measurement of RA flare, the Working Group will identify available validated instruments that capture elements of these domains to enable PRO instrument development. It is anticipated that new additional instruments will need to be developed and validated to appropriately define and measure RA flare.

Another aspect of the use of the term “Flare” likely represents a continuum, so an anchor for flare assessment is required. The anchor must be appropriate to reflect detectable or important change in RA disease activity. An initial assumption was that a clinically relevant flare occurs when RA signs and symptoms worsen in both intensity and duration to the point that a patient requests evaluation, and to the extent that a clinician determines that a change in treatment is appropri-

Table 1. Settings for use of a rheumatoid arthritis flare measure<sup>4</sup>.

---

Clinical Trials
Detecting adequacy of dose/regimen for duration of therapeutic effect — driving to remission (“tight control”)
Aiding dose/regimen optimization — titration and tapering while maintaining remission
Assessing effect of concomitant medications to control oscillating symptoms/signs
Assessing and reporting of episodic disease-worsening as an adverse event
Determining remission as <i>absence</i> of disease flare among other measures

  

Clinical Practice
Facilitating MD-patient communication when considering change in therapy for intermittent disease-worsening
Determining need to change treatment
Assessing patient-specific interventions to control episodic worsening
Enabling assessments to apply “tight control” strategies on an individual patient basis
Assessing episodic disease-worsening
Limiting effect of and disability associated with periodic disease-worsening (e.g., time lost from work)

---

ate<sup>1</sup>. This conceptual definition represents an easily understood standard to identify the range of attributes, or domains that characterize “flare in RA.” It is immediately apparent that such a grounding definition represents only one extreme (e.g., the most severe) of the flare continuum. This operational construct was agreed by consensus at OMERACT 9 for the purpose of initial evaluations of the flare experience as it was identified to represent a feasible anchor for RCT.

### The Critical Role of the Patient Perspective in Defining Flare

PRO are increasingly recognized as a critical component of the assessment of efficacy in clinical trials and clinical practice<sup>20,21</sup>. Thus, involvement of patients has been a key aspect of the OMERACT process, and patient research partners have played an integral role to enable understanding of the totality of the disease experience. For example, patient research partners contributed to the recognition of fatigue as an important domain to evaluate in the assessment of RA disease activity<sup>19,22</sup>.

In our qualitative research with patients, several questions regarding the RA flare experience were identified. First, for patients, there is no consensus on the “meaning of flare” and the context(s) in which the term is used. For example, some of the domains used in describing the flare experience include pain, stiffness, fatigue, functional ability, participation in life activities, sleep, and emotional distress. While it is likely that individual patients can generally distinguish different levels of flare in terms of severity and impact, the metrics that patients use to make this determination are not yet defined. The actions of patients (e.g., self-management) in response to episodic disease worsening have also been poorly quantified, including pharmacologic and nonpharmacologic interventions.

The characteristics of a flare or the threshold at which patients decide to contact a health professional for change in management are also unknown. In turn, the perceived efficacy of different treatments to mitigate flares requires further evaluation. The influence of a patient’s prior level of disease activity and control in their perception of flare is also an important variable that requires integration into the flare concept.

To evaluate these aspects of the flare concept, investigators and patient research partners in our group have conducted qualitative research in 5 countries on 3 continents to better understand the patient’s experience of flare<sup>19</sup>. Several important concepts have thus far emerged: (1) Patients use the term “flare” to refer to several distinct levels of disease experience<sup>19</sup>; (2) Many patients identify a prodromal state that precedes a worse flare; (3) The duration of symptoms and persistence are important qualifiers; and (4) There is a progression from an initial uncertainty as to whether the symptoms experienced are a “normal” fluctuation, or the beginning of disease becoming more unmanageable. There is significant utilization of various strategies of self-management in response to specific symptom clusters. From the patient’s perspective, increasing utilization and ultimately the failure of self-management strategies to maintain control of RA disease activity is an important and particularly disabling aspect of flare in RA. Patients have also identified several key unique features.

### Assessing Validity of a Flare Definition

As introduced earlier, selecting a proper anchor to reflect the “truth” of a flare measure will depend on several likely overlapping features, including a patient self-report of flare that will need to be developed, together with clinical variables (e.g., swollen and tender joints and laboratory parameters) to evaluate both construct and content validity. In initial data-mining exercises in LOS and RCT, we are evaluating whether worsening in patient and physician global assessments of disease can be used as a surrogate for an episodic increase in disease activity that a patient describes as a flare, or if a physician decision to increase or change therapy can be used in initial assessment of a more directed or comprehensive flare tool. It is important to recognize that while measures such as Disease Activity Score 28 or Clinical Disease Activity Index or inverse response criteria (European League Against Rheumatism response and American College of Rheumatology response) may capture disease worsening, they may not be sufficiently sensitive to detect a potentially disabling flare or to accurately measure flare, considering the hetero-

geneity of the patient experience. Importantly, such composite indices may not be as useful for a specific patient's assessment of flare to establish their criterion validity. For example, changes in these indices using improvement cutpoints in the direction of worsening may represent a level that is beyond a patient acceptable symptom state (PASS)<sup>23,24</sup>.

Again considering the patient perspective, there is an essential need to determine the minimal clinically important differences (MCID) in disease worsening, as the MCID in the direction of worsening may be smaller than for improvement, as has been demonstrated for the Medical Outcome Study Short-Form 36<sup>25</sup>. Patients perceive and report attributes of their disease relative to baseline disease severity, response to treatment, and possibly other factors. A patient's tolerance for a small degree of worsening may be greater or lesser, depending on a variety of factors including coping skills and confidence after living with RA for a period of time, often with an acceptance (perhaps incorrectly) that episodic fluctuations of disease activity are part and parcel of their disease experience<sup>25</sup>. It is also possible that once patients have experienced significant improvement from a highly active disease state, they may perceive worsening sooner<sup>25,26</sup>.

### Considerations in Operationalizing a Flare Definition for RCT

Because an RA flare does not represent a single point in time but is the persistence of symptoms in spite of attempts at management, there is a need to determine how the duration of symptoms and severity of symptoms interact. As well as overall increases in disease activity, there may be instances in which a single swollen joint becomes completely incapacitating, thus requiring a change in treatment. Central to each scenario are both the intensity and the duration of symptoms. Thus, in assessing flare in the context of an RCT, patient self-report of flare should trigger evaluation of the key domains in terms of their duration. Unfortunately, collecting such data at the time of a scheduled visit requires effective recall, which is recognized to be relatively inaccurate; including assessment of duration in a definition of flare is a problem that will need to be addressed in this research.

While a validated flare-specific instrument would be ideal, the development of such a tool will proceed with evaluation of the existing instruments at the time of a flare, rather than in retrospect. Conceptually, because RA flare or worsening RA may also be reported as an adverse event, it is important to develop a means to assess intensity that will allow quantification of such episodes, perhaps in terms of the action taken and the impact on the patient, as proposed in the Common Toxicity Criteria RCTC version 2.0<sup>8</sup>. Patients and clinicians may use short courses of corticosteroids or increases in NSAID as an initial treatment for a flare, and it is important to accurately capture such self-management methods together with the signs and symptoms that led to the decision for such an intervention.

### Is Remission Also Defined by the Absence of Flares?

A final concept to introduce is that flare is a real and consequential part of disease. Often unpredictable and at times disabling, these episodes are very real. The current goal, to treat RA to attain a low disease activity state or remission, fails to take into account the potential of ongoing flares to represent the persistence of disease activity, which is not reflected in our current outcome measurements as goals of therapy. Establishing a framework to assess flare will permit further exploration of the criterion validity of remission based on current outcome measures against a new standard. Integration of measures such as the RA Impact of Disease (RAID) questionnaire and concepts such as the patient acceptable symptom state are also critical to evaluate in relationship to the assessment of flare as applied to low disease activity states<sup>23,24,27</sup>.

### Next Steps

This hypothesized conceptual framework to evaluate RA flare will serve as the basis for a process to develop an outcome measure that will quantify this complex RA disease experience<sup>28</sup>. Our preliminary anchoring definition, based on worsening disease activity that leads to an assessment for a change in therapy, will allow data-mining to be conducted in retrospective datasets, as well as in prospective studies that will actually measure intensity and the influence of flare for the RA patient. A particular RCT context in which the components of a preliminary flare measure can be incorporated includes studies of patients aimed at achieving remission based on current validated disease measures<sup>29</sup>. These remission studies could incorporate a flare assessment to determine the occurrence, intensity, duration, and frequency of flares.

Alternatively, or additionally, studies could seek to determine the optimal maintenance dosing regimen, and the ability to achieve drug-free remission, including algorithms for blinded dose reduction, tapering, or elimination; these studies would include the number of patients who successfully reduce therapy without flare, experience increasing time to flare, or experience a number of flares (this may include both intensity and duration).

The current conceptual model will be refined as such additional data are integrated into defining the concept of RA flare. The consistent, continued involvement of experienced and knowledgeable patient research partners enables reality-based testing of the criterion validity of our work, including its relevance across varying cultures.

### Conclusion

A "flare in RA" is a multilayered and complex feature of this chronic, often disabling disease. It is an integral feature of the RA disease process that has hitherto been poorly described or measured. There is an immediate need to develop methods to accurately capture and measure flares and to facilitate the design of RCT incorporating flare as an outcome. Importantly, the quantification of flares and a means to assess their severi-

ty and impact will serve to enhance clinical care for patients with RA. Patients' descriptors of their RA flares include more than joint symptoms or traditionally measured elements of the endpoint core sets used in RCT, LOS, and clinical practice. Some features may be even more important to patients than these standard clinical variables in terms of their effects on function and participation in usual activities. Through qualitative and quantitative research, multiple stakeholders including patient research partners have worked together in the OMER-ACT RA Flare Definition Working Group to conceptualize the flare experience in a manner that encompasses constitutional, physical, functional, psychological, and time-oriented elements. The work of our group will help to improve both clinical trials and clinical care through an expansion of the vocabulary to enhance patient-healthcare provider communication of a potentially disabling aspect of RA.

## ACKNOWLEDGMENT

We are grateful for the participation of patients and health professional participants in focus groups and Delphi exercises.

## APPENDIX

List of study collaborators: The OMERACT RA Flare Definition Working Group: Susan Bartlett, Maarten Boers, Annelies Boonen, Richard Brasington, Peter Brooks, Vivian Bykerk, Jeff Curtis, Bruno Fautrel, Kathleen Ferrell, Niti Goel, Eswar Krishnan, David Magnusson, Lyn Marsh, Diane Moniz, Pam Montie, Tim Shaw, Jasvinder Singh, Josef Smolen, Alan Solinger, Mahboob Rahman, Swati Tole, Jim Witter.

## REFERENCES

- Bingham CO, Pohl C, Woodworth TE, Hewlett SE, May JE, Rahman MU, et al. Developing a standardized definition for disease "Flare" in rheumatoid arthritis. OMERACT 9 Special Interest Group. *J Rheumatol* 2009;36:2335-41.
- Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. *Arthritis Care Res* 2010;62:857-64.
- Petersson IF, Rader T, Tugwell P. OMERACT 10 — Domains session: Domains selection for patient reported outcomes — what to measure? OMERACT 10. (Unpublished pre-conference paper.)
- Bingham CO, Pohl C, Alten R, Christensen R, Choy E, Hewlett S, et al. "Flare" and disease worsening in rheumatoid arthritis: time for definition. *Int J Adv Rheumatol* 2009;7:85-91.
- Bingham CO III, Alten R, Bartlett SJ, Bykerk VP, Brooks PM, Choy E, et al, for the OMERACT RA Flare Definition Working Group. Identifying preliminary domains to detect and measure rheumatoid arthritis flares: Report of the OMERACT 10 RA Flare Workshop. *J Rheumatol* 2011;38:1751-8.
- Bell MJ, Tavares R, Guillemin F, Bykerk VP, Tugwell P, Wells GA. Development of a self-administered early inflammatory arthritis detection tool. *BMC Musculoskel Disord* 2010;11:50.
- Bykerk VP, Solomon D, Bingham CO, Frits M, Iannaccone C, Weinblatt M. The role of objective measures vs. patient reported outcomes (PROs) as a reflection of flares in patients with RA: Results from the Brigham RA Sequential Study (BRASS) [abstract 2636]. *Arthritis Rheum, ACR* 2010.
- Woodworth T, Furst DE, Alten R, Bingham CO, Yocum D, Sloan V, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials. II: the Rheumatology Common Toxicity Criteria v.2.0. *J Rheumatol* 2007;34:1401-14.
- Smolen J, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964-75.
- Yazici Y, Erkan D, Kulman I, Belostocki K, Harrison MJ. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". *Ann Rheum Dis* 2002;61:638-40.
- Van Vollenhoven RF, Brannemark S, Klareskog L. Dose escalation of infliximab in clinical practice: improvements seen may be explained by a regression-like effect. *Ann Rheum Dis* 2004;63:426-30.
- Smolen JS, Keystone EC, Emery P, Breedveld FC, Betteridge N, Burmester G, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66:143-50.
- Mease PJ, Cohen S, Gaylis NB, Chubick A, Kael AT, Greenwald M, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. *J Rheumatol* 2010;37:917-27.
- Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med* 2000;342:763-9.
- Thurlings RM, Vos K, Gerlag DM, Tak PP. Disease activity-guided rituximab therapy in rheumatoid arthritis: the effects of re-treatment in initial nonresponders versus initial responders. *Arthritis Rheum* 2008;58:3657-64.
- Van Vollenhoven RF, Boumpas D, Westhovens R, Brzosko M, Svensson K, Bjerneboe O, et al. Response, remission and flare during early treatment of rheumatoid arthritis with infliximab: The REMARK Study [abstract]. *Ann Rheum Dis* 2010;69 Suppl 3:535.
- Fleischmann RM, Cohen SB, Moreland LW, Schiff M, Mease PJ, Smith DB, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. *Curr Med Res Opin* 2005;21:1181-90.
- Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum* 2006;54:1075-86.
- Hewlett S, Sanderson T, May J, Alten R, Bingham CO III, Cross M, et al. "I'm hurting, I want to kill myself": Rheumatoid arthritis flare is more than a high joint count — an international patient perspective on flare where medical help is sought. *Rheumatology* 2011; May 12 (Epub ahead of print).
- Sanderson T, Morris M, Calnan M, Richards P, Hewlett S. Patient perspective of measuring treatment efficacy: The rheumatoid arthritis patient priorities for pharmacologic interventions outcomes. *Arthritis Care Res* 2010;62:647-56.
- Furst D, Chang H, Ranganath V, Khanna D, Kremer JM, Greenberg J. Defining change in disease activity parameters associated with loss of response over time in RA patients [abstract 1817]. *Arthritis Rheum* 2007;56 Suppl:S709.
- Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, de Wit M, et al. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol* 2007;34:1174-7.
- Kvien TK, Heiberg T, Hagen KB. Minimal clinically important improvement/difference (MCII/MCID) and patient acceptable symptom state (PASS): what do these concepts mean? *Ann Rheum Dis* 2007;66 Suppl III:iii40-iii41.
- Dougados M. It's good to feel better but it's better to feel good... and even better to feel good as soon as possible and for as long as possible [editorial]. *J Rheumatol* 2005;32:1-2.

25. Strand V, Singh J. Newer biologic agents improve health related quality of life and productivity in rheumatoid arthritis. *Drugs* 2010;70:121-45.
26. Aletaha D, Landewé R, Karonitsch T, Bathon J, Boers M, Bombardier C, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Arthritis Rheum* 2008;59:1371-7.
27. Gossec L, Paternotte S, Aanerud GJ, Balanescu A, Boumpas DT, Carmona L, et al. Finalisation and validation of the Rheumatoid Arthritis Impact of Disease (RAID) score, a patient-derived composite measure of impact of rheumatoid arthritis. A EULAR initiative. *Ann Rheum Dis* 2011; [in press].
28. Guidance for industry: Patient-reported outcome measures: use in medical product development to support labeling claims. December 2009. [Internet. Accessed April 6, 2011.] US Department of Health and Human Services, FDA. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>
29. van Tuyl LHD, Vlad SC, Felson DT, Wells G, Boers M. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. *Arthritis Rheum* 2009;61:704-10.