



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**CONCEPT PAPER ON THE NEED FOR REVISION OF THE POINTS TO CONSIDER ON  
THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS OTHER THAN NSAIDS  
IN RHEUMATOID ARTHRITIS (CPMP/EWP/556/95 REV. 1)**

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| <b>KEYWORDS</b> | <i>Rheumatoid arthritis (RA), disease-modifying antirheumatic drugs (DMARD), symptom and structure modification, efficacy variables, endpoints, study design, comparator, early disease</i> |
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## **1. INTRODUCTION**

Since 2003 this guideline has presented guidance for the clinical development of slow-acting anti-rheumatic medicinal products aiming at symptom- and/or structure-modification (*e.g.* DMARDs, biologics) for the treatment of rheumatoid arthritis (RA). In the last years efforts have been made in that field with regard to the development of new products with an improved efficacy profile and novel insights have been gained with respect to the assessment of disease activity, joint damage and disability. Furthermore, new treatment strategies have been established which relate to early therapy, tight control and rapid switching of medication. Accordingly, new EULAR/ACR recommendations have been developed. Therefore several important additions and changes are needed to express the current state of scientific knowledge in this guideline.

## **2. PROBLEM STATEMENT**

The search for improved and meaningful endpoints and study designs adapted to the changed pharmacologic profile of new agents and elaborated treatment strategies has prompted several groups of scientists to develop new recommendations for conducting clinical studies in RA. A need is identified to update the regulatory guidance on the clinical development of medicinal products intended for the treatment of RA.

## **3. DISCUSSION (ON THE PROBLEM STATEMENT)**

The main topics to be discussed when revising the guidance document are:

1. New efficacy variables to assess clinical responses considering the improved efficacy of new biologic agents (*e.g.* (ACR70 response, Disease Activity Score [DAS] remission, and physical function by the Health Assessment Questionnaire [HAQ])) according to the claimed therapeutic indication.
2. Developments in the assessment of structural damage
3. Developments in the assessments of QoL
4. Primary endpoints (alternatives to the ACR 20/50/70% response rates).
5. Choice of comparators including Placebo control for first, second and third line indication.
6. Biologic agents as active comparators.
7. Duration of studies necessary for intended claims of symptom modifying effect, disease modifying effect or for a claim to delay progression of structural damage.
8. Duration of placebo-controlled phase.
9. New study designs (*e.g.* add on, switching, drug free intervals).
10. Study populations: *e.g.* severe RA, early RA, undifferentiated arthritis (and to look at how accurately biomarkers really reflect prognosis)
11. Concept of traditional versus new potential claims.
12. New safety aspects.

## **4. RECOMMENDATION**

It is proposed to revise the current CHMP Points to Consider (PtC) addressing the clinical investigation of medicinal products other than NSAIDs for treatment of RA in order to achieve a European common position on the above-mentioned issues.

## **5. PROPOSED TIMETABLE**

It is anticipated that a new draft CHMP guideline may be available in the 2<sup>nd</sup>/3<sup>rd</sup> Quarter 2010 to be later released for 6 months for external consultation and, thereafter, finalised within 6 months.

## **6. RESOURCE REQUIREMENTS FOR PREPARATION**

The preparation of this revision of the guideline will involve the EWP. It is anticipated that at least one plenary session discussions at the EWP will be needed.

## **7. IMPACT ASSESSMENT (ANTICIPATED)**

The revision of the PtC on clinical investigation of medicinal products other than NSAIDs in RA will be helpful to achieve consensus in the evaluation of such products by regulatory authorities. Furthermore, it is expected that such guidance document would improve quality and comparability of submitted studies by pharmaceutical industries.

## **8. INTERESTED PARTIES**

It is envisioned to contact EULAR (European League Against Rheumatism) and GREES (Group for the Respect of Ethics and Excellence in Science).

## 9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. *Arthritis Rheum* 2007; 57(2):193-202.
2. Aletaha D, Smolen JS. Threats to validity of observational studies on disease-modifying antirheumatic drug therapies for rheumatoid arthritis: new aspects after the fall of the pyramid and the rise of new therapeutics. *Curr Rheumatol Rep* 2003; 5(6):409-412.
3. Aletaha D, Smolen JS. DMARD use in early rheumatoid arthritis. Lessons from observations in patients with established disease. *Clin Exp Rheumatol* 2003; 21(5 Suppl 31):S169-S173.
4. Aletaha D, Eberl G, Nell VP, Machold KP, Smolen JS. Attitudes to early rheumatoid arthritis: changing patterns. Results of a survey. *Ann Rheum Dis* 2004; 63(10):1269-1275.
5. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005; 7(4):R796-R806.
6. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005; 23(5 Suppl 39):S100-S108.
7. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. *Arthritis Rheum* 2005; 52(9):2625-2636.
8. Aletaha D, Breedveld FC, Smolen JS. The need for new classification criteria for rheumatoid arthritis. *Arthritis Rheum* 2005; 52(11):3333-3336.
9. Aletaha D, Ward MM. Duration of rheumatoid arthritis influences the degree of functional improvement in clinical trials. *Ann Rheum Dis* 2006; 65(2):227-233.
10. Aletaha D. Pooled indices to measure rheumatoid arthritis activity: a good reflection of the physician's mind? *Arthritis Res Ther* 2006; 8(1):102.
11. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components. *Arthritis Rheum* 2006; 54(9):2784-2792.
12. Aletaha D, Smolen JS. Remission of rheumatoid arthritis: should we care about definitions? *Clin Exp Rheumatol* 2006; 24(6 Suppl 43):S-51.
13. Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. *Rheum Dis Clin North Am* 2006; 32(1):9-44, vii.
14. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. *Arthritis Rheum* 2007; 56(10):3226-3235.
15. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. *Best Pract Res Clin Rheumatol* 2007; 21(4):663-675.
16. Aletaha D, Landewe 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(10):1371-1377.
17. Aletaha D, Landewe 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. *Ann Rheum Dis* 2008; 67(10):1360-1364.
18. Aletaha D, Funovits J, Smolen JS. The importance of reporting disease activity states in rheumatoid arthritis clinical trials. *Arthritis Rheum* 2008; 58(9):2622-2631.

19. Aletaha D, Strand V, Smolen JS, Ward MM. Treatment-related improvement in physical function varies with duration of rheumatoid arthritis: a pooled analysis of clinical trial results. *Ann Rheum Dis* 2008; 67(2):238-243.
20. Aletaha D, Huizinga TW. The use of data from early arthritis clinics for clinical research. *Best Pract Res Clin Rheumatol* 2009; 23(1):117-123.
21. Aletaha D, Funovits J, Breedveld FC, Sharp J, Segurado O, Smolen JS. Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. *Arthritis Rheum* 2009; 60(5):1242-1249.
22. Aletaha D, Funovits J, Ward MM, Smolen JS, Kvien TK. Perception of improvement in patients with rheumatoid arthritis varies with disease activity levels at baseline. *Arthritis Rheum* 2009; 61(3):313-320.
23. Bakker MF, Jacobs JW, Verstappen SM, Bijlsma JW. Tight control in the treatment of rheumatoid arthritis: efficacy and feasibility. *Ann Rheum Dis* 2007; 66 Suppl 3:iii56-iii60.
24. Bijlsma JW, Boers M, Saag KG, Furst DE. Glucocorticoids in the treatment of early and late RA. *Ann Rheum Dis* 2003; 62(11):1033-1037.
25. Boers M, Ramsden M. Long acting drug combinations in rheumatoid arthritis: a formal overview. *J Rheumatol* 1991; 18(3):316-324.
26. Boers M, Guyatt GH, Oxman AD. Combined effect size: comment on the metaanalysis of second-line drugs in rheumatoid arthritis. *Arthritis Rheum* 1991; 34(10):1342-1343.
27. Boers M. Low-dose prednisone in rheumatoid arthritis patients: placebo treatment? *Arthritis Rheum* 1991; 34(4):501-502.
28. Boers M, Tugwell P. The validity of pooled outcome measures (indices) in rheumatoid arthritis clinical trials. *J Rheumatol* 1993; 20(3):568-574.
29. Boers M. International consensus on which measures to use in rheumatoid arthritis clinical trials. *Neth J Med* 1993; 43(1-2):55-58.
30. Boers M, Tugwell P, Felson DT, van Riel PL, Kirwan JR, Edmonds JP et al. World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials. *J Rheumatol Suppl* 1994; 41:86-89.
31. Boers M, Felson DT. Clinical measures in rheumatoid arthritis: which are most useful in assessing patients? *J Rheumatol* 1994; 21(9):1773-1774.
32. Boers M, van Riel PL, Felson DT, Tugwell P. Assessing the activity of rheumatoid arthritis. *Baillieres Clin Rheumatol* 1995; 9(2):305-317.
33. Boers M. The validity of radiography as outcome measure in rheumatoid arthritis. *J Rheumatol* 1995; 22(9):1783-1786.
34. Boers M, Verhoeven AC, van der LS. [Combination therapy in early rheumatoid arthritis: the COBRA study]. *Ned Tijdschr Geneesk* 1997; 141(50):2428-2432.
35. Boers M, Verhoeven AC, Markusse HM, Van de Laar MA, Westhovens R, Van Denderen JC et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350(9074):309-318.
36. Boers M, Brooks P, Strand CV, Tugwell P. The OMERACT filter for Outcome Measures in Rheumatology. *J Rheumatol* 1998; 25(2):198-199.
37. Boers M. Combination therapy in rheumatoid arthritis. *Lancet* 1999; 354(9182):952.
38. Boers M. Demonstration of response in rheumatoid arthritis patients who are nonresponders according to the American College of Rheumatology 20% criteria: the paradox of beneficial

- treatment effects in nonresponders in the ATTRACT trial. *Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy*. *Arthritis Rheum* 2001; 44(11):2703-2704.
39. Boers M. Rheumatoid arthritis. Treatment of early disease. *Rheum Dis Clin North Am* 2001; 27(2):405-14, x.
  40. Boers M, Kostense PJ, Verhoeven AC, van der LS. Inflammation and damage in an individual joint predict further damage in that joint in patients with early rheumatoid arthritis. *Arthritis Rheum* 2001; 44(10):2242-2246.
  41. Boers M, Verhoeven AC, van der LS. American College of Rheumatology criteria for improvement in rheumatoid arthritis should only be calculated from scores that decrease on improvement. *Arthritis Rheum* 2001; 44(5):1052-1055.
  42. Boers M. Combination treatment in autoimmune diseases. *Methodology of combination trials*. Springer Semin Immunopathol 2001; 23(1-2):27-33.
  43. Boers M, van der Heijde DM. Prevention or retardation of joint damage in rheumatoid arthritis: issues of definition, evaluation and interpretation of plain radiographs. *Drugs* 2002; 62(12):1717-1724.
  44. Boers M. Understanding the window of opportunity concept in early rheumatoid arthritis. *Arthritis Rheum* 2003; 48(7):1771-1774.
  45. Boers M, Anderson JJ, Felson DT. Deriving an operational definition of low disease activity state in rheumatoid arthritis. *J Rheumatol* 2003; 30(5):1112-1114.
  46. Boers M, Nurmohamed MT, Doelman CJ, Lard LR, Verhoeven AC, Voskuyl AE et al. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003; 62(9):842-845.
  47. Boers M. Add-on or step-up trials for new drug development in rheumatoid arthritis: a new standard? *Arthritis Rheum* 2003; 48(6):1481-1483.
  48. Boers M. Evidence for interaction between disease severity and comorbidity in rheumatoid arthritis? comment on the article by Navarro-Cano et al. *Arthritis Rheum* 2004; 50(5):1695-1697.
  49. Boers M. Use of the American College of Rheumatology N (ACR-N) index of improvement in rheumatoid arthritis: argument in opposition. *Arthritis Rheum* 2005; 52(6):1642-1645.
  50. Boers M, Brooks P, Simon LS, Strand V, Tugwell P. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Clin Exp Rheumatol* 2005; 23(5 Suppl 39):S10-S13.
  51. Boers M. COBRA combination therapy in daily practice--getting back to the future. *Rheumatology (Oxford)* 2008; 47(1):1-2.
  52. Boers M. A call for pragmatic treatment trials in rheumatoid arthritis. *Nat Clin Pract Rheumatol* 2008; 4(6):292-293.
  53. Boers M. Missing data in trials: do we have to keep carrying the last observation forward? *Arthritis Rheum* 2008; 59(1):2-3.
  54. Boers M. The time has come to limit the placebo period in rheumatoid arthritis trials to 3 months: A systematic comparison of 3- and 6-month response rates in trials of biologic agents. *Ann Rheum Dis* 2009; published online 22 Sept 2009.
  55. Boers M. A new design for registration trials in rheumatoid arthritis allowing secondary head-to-head comparisons with standard of care treatment including biologics. *Ann Rheum Dis* 2009; in press.
  56. Braun J, Sieper J, van der Heijde D. Definition of discontinuation of anti-tumour necrosis factor therapy in rheumatoid arthritis: a preliminary proposal. *Ann Rheum Dis* 2003; 62(10):1023-1024.

57. Breedveld FC, Han C, Bala M, van der Heijde D, Baker D, Kavanaugh AF et al. Association between baseline radiographic damage and improvement in physical function after treatment of patients with rheumatoid arthritis. *Ann Rheum Dis* 2005; 64(1):52-55.
58. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, Sharp J, Perez JL, Spencer-Green GT. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*. 2006;54(1):26-37.
59. Bruynesteyn K, van der Heijde D, Boers M, Lassere M, Boonen A, Edmonds J et al. Minimal clinically important difference in radiological progression of joint damage over 1 year in rheumatoid arthritis: preliminary results of a validation study with clinical experts. *J Rheumatol* 2001; 28(4):904-910.
60. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. *Arthritis Rheum* 2002; 46(4):913-920.
61. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H et al. Detecting radiological changes in rheumatoid arthritis that are considered important by clinical experts: influence of reading with or without known sequence. *J Rheumatol* 2002; 29(11):2306-2312.
62. Bruynesteyn K, van der Heijde D, Boers M, Verhoeven A, Boonen A, van der LS. Contribution of progression of erosive damage in previously eroded joints in early rheumatoid arthritis trials: COBRA trial as an example. *Arthritis Rheum* 2002; 47(5):532-536.
63. Bruynesteyn K, van der Heijde D, Boers M, van der LS, Lassere M, van d, V. The Sharp/van der Heijde method out-performed the Larsen/Scott method on the individual patient level in assessing radiographs in early rheumatoid arthritis. *J Clin Epidemiol* 2004; 57(5):502-512.
64. Bruynesteyn K, Landewe R, van der LS, van der Heijde D. Radiography as primary outcome in rheumatoid arthritis: acceptable sample sizes for trials with 3 months' follow up. *Ann Rheum Dis* 2004; 63(11):1413-1418.
65. Bruynesteyn K, Boers M, Kostense P, van der LS, van der Heijde D. Deciding on progression of joint damage in paired films of individual patients: smallest detectable difference or change. *Ann Rheum Dis* 2005; 64(2):179-182.
66. Calguneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I et al. Combination therapy versus monotherapy for the treatment of patients with rheumatoid arthritis. *Clin Exp Rheumatol* 1999; 17(6):699-704.
67. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66(1):34-45.
68. Dougados M, Aletaha D, van Riel P. Disease activity measures for rheumatoid arthritis. *Clin Exp Rheumatol* 2007; 25(5 Suppl 46):S22-S29.
69. Dougados M, Schmidely N, Le Bars M, Lafosse C, Schiff M, Smolen JS et al. Evaluation of different methods used to assess disease activity in rheumatoid arthritis: analyses of abatacept clinical trial data. *Ann Rheum Dis* 2009; 68(4):484-489.
70. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; 372(9636):375-382.

71. Emery P, McInnes IB, van Vollenhoven R, Kraan MC. Clinical identification and treatment of a rapidly progressing disease state in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2008; 47(4):392-398.
72. Fautrel B, Pham T, Mouterde G, Le L, X, Goupille P, Guillemin F et al. Recommendations of the French Society for Rheumatology regarding TNFalpha antagonist therapy in patients with rheumatoid arthritis. *Joint Bone Spine* 2007; 74(6):627-637.
73. Fautrel B, Guillemin F, Meyer O, de Bandt M, Berthelot JM, Flipo RM et al. Choice of second-line disease-modifying antirheumatic drugs after failure of methotrexate therapy for rheumatoid arthritis: a decision tree for clinical practice based on rheumatologists' preferences. *Arthritis Rheum* 2009; 61(4):425-434.
74. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum* 1993; 36(6):729-740.
75. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38(6):727-735.
76. Felson DT, Furst DE, Boers M. Rationale and strategies for reevaluating the ACR20. *J Rheumatol* 2007; 34(5):1184-1187.
77. Ferraccioli GF, Gremese E, Tomietto P, Favret G, Damato R, Di Poi E. Analysis of improvements, full responses, remission and toxicity in rheumatoid patients treated with step-up combination therapy (methotrexate, cyclosporin A, sulphasalazine) or monotherapy for three years. *Rheumatology (Oxford)* 2002; 41(8):892-898.
78. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, Fischkoff SA, Chartash EK. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol.* 2003;30(12):2563-2571.
79. Garnero P, Landewe R, Boers M, Verhoeven A, van der LS, Christgau S et al. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. *Arthritis Rheum* 2002; 46(11):2847-2856.
80. Genovese MC, Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; 46(6):1443-1450.
81. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. *Arthritis Rheum* 2004; 50(5):1412-1419.
82. Giles JT, Mease P, Boers M, Bresnihan B, Conaghan PG, Heald A et al. Assessing single joints in arthritis clinical trials. *J Rheumatol* 2007; 34(3):641-647.
83. Goekoop-Ruiterman YP, Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum* 2008; 58(2 Suppl):S126-S135.
84. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004; 364(9430):263-269.

85. Gulfe A, Aletaha D, Saxne T, Geborek P. Disease activity level, remission and response in established rheumatoid arthritis: performance of various criteria sets in an observational cohort, treated with anti-TNF agents. *BMC Musculoskelet Disord* 2009; 10:41.
86. Hafstrom I, Albertsson K, Boonen A, van der Heijde D, Landewe R, Svensson B. Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open 2-year continuation study. *Ann Rheum Dis* 2009; 68(4):508-513.
87. Heiberg T, Kvien TK, Mowinckel P, Aletaha D, Smolen JS, Hagen KB. Identification of disease activity and health status cut-off points for the symptom state acceptable to patients with rheumatoid arthritis. *Ann Rheum Dis* 2008; 67(7):967-971.
88. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis* 2007; 66(12):1560-1567.
89. Kapral T, Stamm T, Machold KP, Montag K, Smolen JS, Aletaha D. Methotrexate in rheumatoid arthritis is frequently effective, even if re-employed after a previous failure. *Arthritis Res Ther* 2006; 8(2):R46.
90. Kapral T, Demoschnig F, Machold KP, Stamm T, Schoels M, Smolen JS et al. Remission by composite scores in rheumatoid arthritis: are ankles and feet important? *Arthritis Res Ther* 2007; 9(4):R72.
91. Karonitsch T, Aletaha D, Boers M, Bombardieri S, Combe B, Dougados M et al. Methods of deriving EULAR/ACR recommendations on reporting disease activity in clinical trials of patients with rheumatoid arthritis. *Ann Rheum Dis* 2008; 67(10):1365-1373.
92. Kavanaugh A, Klareskog L, van der Heijde D, Li J, Freundlich B, Hooper M. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. *Ann Rheum Dis* 2008; 67(10):1444-1447.
93. Kavanaugh A. Therapy: Guidelines in rheumatology: quo vadis? *Nat Rev Rheumatol* 2009; 5(8):423-424.
94. Kay J, Westhovens R. Methotrexate: the gold standard without standardisation. *Ann Rheum Dis* 2009; 68(7):1081-1082.
95. Korpela M, Laasonen L, Hannonen P, Kautiainen H, Leirisalo-Repo M, Hakala M et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the FIN-RACo study. *Arthritis Rheum* 2004; 50(7):2072-2081.
96. Landewe R, van der Heijde D. Presentation and analysis of radiographic data in clinical trials and observational studies. *Ann Rheum Dis* 2005; 64 Suppl 4:iv48-iv51.
97. Landewe RB, Boers M, Verhoeven AC, Westhovens R, Van de Laar MA, Markusse HM et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. *Arthritis Rheum* 2002; 46(2):347-356.
98. Landewe RB, Boers M, van der Heijde DM. How to interpret radiological progression in randomized clinical trials? *Rheumatology (Oxford)* 2003; 42(1):2-5.
99. Machold KP, Nell V, Stamm T, Aletaha D, Smolen JS. Early rheumatoid arthritis. *Curr Opin Rheumatol* 2006; 18(3):282-288.
100. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. *Rheumatology (Oxford)* 2007; 46(2):342-349.
101. Makinen H, Kautiainen H, Hannonen P, Sokka T. Is DAS28 an appropriate tool to assess remission in rheumatoid arthritis? *Ann Rheum Dis* 2005; 64(10):1410-1413.

102. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. *Rheumatology (Oxford)* 2007; 46(6):975-979.
103. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. *Lancet* 1999; 353(9164):1568-1573.
104. O'Dell JR, Haire CE, Erikson N, Drymalski W, Palmer W, Eckhoff PJ et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; 334(20):1287-1291.
105. O'Dell JR, Leff R, Paulsen G, Haire C, Mallek J, Eckhoff PJ et al. Treatment of rheumatoid arthritis with methotrexate and hydroxychloroquine, methotrexate and sulfasalazine, or a combination of the three medications: results of a two-year, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46(5):1164-1170.
106. Pham B, Cranney A, Boers M, Verhoeven AC, Wells G, Tugwell P. Validity of area-under-the-curve analysis to summarize effect in rheumatoid arthritis clinical trials. *J Rheumatol* 1999; 26(3):712-716.
107. Pincus T, Kavanaugh A, Aletaha D, Smolen J. Complexities in defining remission in rheumatic diseases. *Clin Exp Rheumatol* 2006; 24(6 Suppl 43):S-6.
108. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Julkunen H et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. *Arthritis Rheum* 2004; 50(1):55-62.
109. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M et al. Early suppression of disease activity is essential for maintenance of work capacity in patients with recent-onset rheumatoid arthritis: five-year experience from the FIN-RACo trial. *Arthritis Rheum* 2005; 52(1):36-41.
110. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008; 59(6):762-784.
111. Saleem B, Mackie S, Quinn M, Nizam S, Hensor E, Jarrett S et al. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? *Ann Rheum Dis* 2008; 67(8):1178-1180.
112. Schoels M, Kapral T, Stamm T, Smolen JS, Aletaha D. Step-up combination versus switching of non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a retrospective observational study. *Ann Rheum Dis* 2007; 66(8):1059-1065.
113. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijckens K et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009; 68(6):797-804.
114. Smolen JS, Emery P. Efficacy and safety of leflunomide in active rheumatoid arthritis. *Rheumatology (Oxford)* 2000; 39 Suppl 1:48-56.
115. Smolen JS, Breedveld FC, Schiff MH, Kalden JR, Emery P, Eberl G et al. A simplified disease activity index for rheumatoid arthritis for use in clinical practice. *Rheumatology (Oxford)* 2003; 42(2):244-257.
116. Smolen JS, Aletaha D, Machold KP. Therapeutic strategies in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol* 2005; 19(1):163-177.
117. Smolen JS, Aletaha D, Keystone E. Superior efficacy of combination therapy for rheumatoid arthritis: fact or fiction? *Arthritis Rheum* 2005; 52(10):2975-2983.
118. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet* 2007; 370(9602):1861-1874.

119. Smolen JS, Aletaha D. Activity assessments in rheumatoid arthritis. *Curr Opin Rheumatol* 2008; 20(3):306-313.
120. Smolen JS, Aletaha D. Strengths and limitations of a systematic review on DMARDs for rheumatoid arthritis. *Nat Clin Pract Rheumatol* 2008; 4(6):296-297.
121. Smolen JS, Aletaha D, Grisar J, Redlich K, Steiner G, Wagner O. The need for prognosticators in rheumatoid arthritis. Biological and clinical markers: where are we now? *Arthritis Res Ther* 2008; 10(3):208.
122. Smolen JS, Aletaha D, Grisar JC, Stamm TA, Sharp JT. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. *Ann Rheum Dis* 2009.
123. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 2009; 68(6):823-827.
124. Smolen JS, Aletaha D, Steiner G. Does damage cause inflammation? Revisiting the link between joint damage and inflammation. *Ann Rheum Dis* 2009; 68(2):159-162.
125. Smolen JS, Aletaha D, Grisar JC, Stamm TA, Sharp JT. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. *Ann Rheum Dis* 2009.
126. Soubrier M, Dougados M. How to assess early rheumatoid arthritis in daily clinical practice. *Best Pract Res Clin Rheumatol* 2005; 19(1):73-89.
127. Soubrier M, Dougados M. Selecting criteria for monitoring patients with rheumatoid arthritis. *Joint Bone Spine* 2005; 72(2):129-134.
128. Soubrier M, Zerkak D, Gossec L, Ayral X, Roux C, Dougados M. Which variables best predict change in rheumatoid arthritis therapy in daily clinical practice? *J Rheumatol* 2006; 33(7):1243-1246.
129. Soubrier M, Puechal X, Sibilia J, Mariette X, Meyer O, Combe B et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. *Rheumatology (Oxford)* 2009.
130. Suresh E, Lambert CM. Combination treatment strategies in early rheumatoid arthritis. *Ann Rheum Dis* 2005; 64(9):1252-1256.
131. van der Bijl AE, Goekoop-Ruiterman YP, Vries-Bouwstra JK, Ten Wolde S, Han KH, van Krugten MV et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. *Arthritis Rheum* 2007; 56(7):2129-2134.
132. van der Helm-van Mil AH, le Cessie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum* 2007; 56(2):433-440.
133. van der Helm-van Mil AH, Detert J, le Cessie S, Filer A, Bastian H, Burmester GR et al. Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making. *Arthritis Rheum* 2008; 58(8):2241-2247.
134. van der Heijde D, Simon L, Smolen J, Strand V, Sharp J, Boers M et al. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a roundtable discussion. *Arthritis Rheum* 2002; 47(2):215-218.
135. van der Heijde D, Klareskog L, Boers M, Landewe R, Codreanu C, Bolosiu HD et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. *Ann Rheum Dis* 2005; 64(11):1582-1587.

136. van der Heijde D, Klareskog L, Singh A, Tornero J, Melo-Gomes J, Codreanu C et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006; 65(3):328-334.
137. van der Heijde D, Burmester G, Melo-Gomes J, Codreanu C, Mola EM, Pedersen R et al. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. *Ann Rheum Dis* 2008; 67(2):182-188.
138. van der Heijde D, Landewe R, van Vollenhoven R, Fatenejad S, Klareskog L. Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial. *Ann Rheum Dis* 2008; 67(9):1267-1270.
139. van der Heijde D, Burmester G, Melo-Gomes J, Codreanu C, Martin ME, Pedersen R et al. Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. *Ann Rheum Dis* 2009; 68(7):1113-1118.
140. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J, Tornero-Molina J, Wajdula J, Pedersen R, Fatenejad S; TEMPO Study Investigators. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum.* 2006;54(4):1063-1074.
141. van der Woude D, Young A, Jayakumar K, Mertens BJ, Toes RE, van der Heijde D et al. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. *Arthritis Rheum* 2009; 60(8):2262-2271.
142. van Dongen H, van Aken J, Lard LR, Visser K, Roday HK, Hulsmans HM et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2007; 56(5):1424-1432.
143. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. *J Rheumatol* 1999; 26(3):705-711.
144. van Tuyl LH, Lems WF, Voskuyl AE, Kerstens PJ, Garnero P, Dijkmans BA et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. *Ann Rheum Dis* 2008; 67(11):1574-1577.
145. van Tuyl LH, Plass AM, Lems WF, Voskuyl AE, Kerstens PJ, Dijkmans BA et al. Discordant perspectives of rheumatologists and patients on COBRA combination therapy in rheumatoid arthritis. *Rheumatology (Oxford)* 2008; 47(10):1571-1576.
146. van Tuyl LH, Boers M, Lems WF, Landewe RB, Han H, van der LS et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. *Ann Rheum Dis* 2009.
147. van Tuyl LH, 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(5):704-710.
148. Visser H, Hazes JM, Luime J. The clinical relevance of a prediction rule for disease outcome in patients with undifferentiated arthritis: comment on the article by van der Helm-van Mil et al. *Arthritis Rheum* 2009; 60(7):2208-2209.
149. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad

- international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009; 68(7):1086-1093.
150. Voskuyl AE, Boers M. Can progression of radiographic joint damage be predicted early in rheumatoid arthritis? *J Rheumatol* 2003; 30(5):905-907.
  151. Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. *Arthritis Rheum* 2008; 58(5):1293-1298.
  152. Welch V, Singh G, Strand V, Fries J, Boers M, Ramey D et al. Patient based method of assessing adverse events in clinical trials in rheumatology: the revised Stanford Toxicity Index. *J Rheumatol* 2001; 28(5):1188-1191.
  153. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis* 2009; 68(6):954-960.
  154. Wells GA, Boers M, Shea B, Brooks PM, Simon LS, Strand CV et al. Minimal disease activity for rheumatoid arthritis: a preliminary definition. *J Rheumatol* 2005; 32(10):2016-2024.
  155. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. *Ann Rheum Dis* 2009.
  156. Wolfe F, Lassere M, van der Heijde D, Stucki G, Suarez-Almazor M, Pincus T et al. Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. *J Rheumatol* 1999; 26(2):484-489.
  157. Wolfe F, Rasker JJ, Boers M, Wells GA, Michaud K. Minimal disease activity, remission, and the long-term outcomes of rheumatoid arthritis. *Arthritis Rheum* 2007; 57(6):935-942.
  158. Wolfe F, Boers M, Felson D, Michaud K, Wells GA. Remission in rheumatoid arthritis: physician and patient perspectives. *J Rheumatol* 2009; 36(5):930-933.