Design and Conduct of Clinical Trials in Osteoarthritis: Preliminary Recommendations from a Task Force of the Osteoarthritis Research Society

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ABSTRACT. In 1994, a combined committee of the World Health Organization and the International League of Associations for Rheumatology published recommendations for clinical trials for 2 classes of agents for treatment of osteoarthritis (OA) that relieved symptoms but differed in their onset and duration of response, and a third class of agents that may alter the disease process. Recently, the European Group for the Respect of Ethics and Excellence in Science made recommendations for methods to be used in the registration of drugs for OA. Following the 2nd international meeting of the Osteoarthritis Research Society in December 1994, a task force was convened to develop recommendations for the design and conduct of clinical trials in patients with OA. The Task Force had several meetings over the past 16 months, resulting in the preliminary recommendations summarized here. (*J Rheumatol 1997;24:792–4*)

Key Indexing Terms:
OSTEOARTHRITIS CLINICAL TRIALS TREATMENT
OUTCOME AND PROCESS ASSESSMENT

The approach to the conduct of clinical trials in patients with osteoarthritis (OA) has evolved over the past decade[1]. In 1994, a combined committee of the World Health Organization and the International League of Associations for Rheumatology published recommendations that defined 2 classes of agents that relieved symptoms but differed in their onset and duration of response, and a third class of agents that may alter the disease process[2]. Recently, the European Group for the Respect of Ethics and Excellence in Science has made recommendations for methods to be used in the registration of drugs for OA[3]. Following the Second International meeting of the Osteoarthritis Research Society in December 1994, a task force was convened to develop recommendations for the design and conduct of clinical trials in patients with OA. The task force had several meetings over 16 months resulting in preliminary recommendations presented at the OMERACT III conference held in Cairns, Australia, in April 1996. The final report[4] of the task force followed a meeting in Washington, DC, in May 1996. This brief report summarizes highlights of preliminary recommendations.

OBJECTIVES OF TREATMENTS OF OA

Treatments for OA may affect symptoms and/or modify joint structure. Design of clinical trials will depend on both the mechanism of action of the treatment and the expected response. Thus, for trials of agents that affect symptoms, patients who enter these trials will have symptomatic OA, and relief of pain will be the primary outcome assessed. The duration of the trial will be determined by the anticipated time to onset of the effects of the agent; the task force does not feel the need to create separate guidelines for agents with rapid versus slow onset of symptom relief.

Treatments designed to modify joint structure may either prevent the development of OA and/or prevent, retard, or reverse the progression of established OA. Drugs attributed such an effect are termed "disease modifying osteoarthritis drugs." The primary outcome assessed in these trials should be joint morphology; the optimal method used to measure joint morphology has yet to be determined. As with trials of symptomatic treatments, the duration of the trial will be determined by the anticipated time to onset of the effects of the agent; it is expected that such trials will be a minimum of 2 years' duration. In patients with established OA, relief of symptoms may accompany alteration in the rate of progression of structural changes; such symptomatic effects, however, would be considered secondary outcomes in these trials.

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DESIGN CONSIDERATIONS FOR TRIALS IN OA

Patients who enter trials of symptomatic agents should fulfil classification criteria for OA, such as those published by the American College of Rheumatology[5–7]. Patient populations should be homogeneous with respect to joint group affected and should have idiopathic OA; if patients with secondary OA are studied, the underlying condition(s) should be specified.

Patients entering trials of symptomatic therapy should have pain of at least mild intensity; those entering trials of disease modifying agents should either be free of OA if the agent is being evaluated for preventive effects, or have mild to moderate OA if the agent is being evaluated for effects on the rate of progression. As noted, the presence of symptoms is not required at time of entry into trials of potential disease modifying agents.

Detailed inclusion and exclusion criteria should be specified in each protocol. The patient's history of OA, including joint group(s) involved, duration of disease, prior use of medications including intraarticular agents, surgical procedures including arthroscopy, and physiotherapy including assistive devices, should be recorded. In addition to a general physical examination, an examination of the affected joint(s) should include evidence of joint deformity and the presence of joint effusion; although it is important to record this information at baseline, it is not felt that these measures have the necessary validity, reliability, and sensitivity to change to be used as outcome measures in trials.

Statistical issues relevant to design and analysis of clinical trials have been reviewed elsewhere[8].

OUTCOME MEASURES IN TRIALS OF OA

A study should have a clearly defined primary outcome variable; several secondary outcome variables may also be measured. For trials of symptomatic agents, pain should be the primary outcome variable. Presently, the 5 item pain scale included in the Western Ontario and McMaster (WOMAC) Osteoarthritis Index is widely used in clinical trials; this instrument has been shown to be valid, reliable, and sensitive to change in patients with OA of the hip and/or knee[9]. Secondary outcome measures to be included in trials of symptomatic agents include functional disability, measured using either the 17 item function scale included in the WOMAC Osteoarthritis Index or the Algofunctional Index in patients with OA of the hip and/or knee[10], the patient's and examiner's opinions of global status, self-reported quality of life, and performance based measures of function. Specific recommendations for instruments to assess quality of life or tests to assess functional performance cannot be made at this time.

For trials of disease modifying agents, a measure of joint morphology should be the primary outcome variable. These measures include imaging and/or direct visualization with arthroscopy[11]. At present, radiography is the preferred method of imaging; recommendations for standardization of radiographic methods in clinical trials[12] and use of atlases for central reading of radiographs[13] have been published. Studies may use either chondrometry or digitization to measure interbone distance as a proxy for joint space narrowing[14,15]. Although magnetic resonance imaging can detect abnormalities of articular cartilage and subchondral bone[16], this technique has not yet been validated in longitudinal studies of patients with OA. Secondary outcome measures in trials of disease modifying agents include those measures used in trials of symptomatic therapy.

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REFERENCES

1. Altman RD, Hochberg MC: Degenerative joint disease. *Clin Rheum Dis 1983;*9:681–93.
2. Lequesne M, Brandt K, Bellamy N, *et al:* Guidelines for testing slow acting drugs in osteoarthritis. *J Rheumatol 1994,*(suppl 41)21:65–73.
3. Dougados M, Devogelaer JP, Annefeld M, *et al:* Recommendations for the registration of drugs used in the treatment of osteoarthritis. *Ann Rheum Dis 1996;*55:552–7.
4. Altman RD, Brandt KD, Hochberg MC, Moskowitz RM, for the Task Force: Design and conduct of clinical trials in osteoarthritis: Recommendations from a task force of the Osteoarthritis Research Society. *Osteoarthritis Cartilage 1996;*4:217–43.
5. Altman R, Asch E, Bloch D, *et al:* Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. *Arthritis Rheum 1986;*29:1039–49.
6. Altman R, Alarcon G, Appelrouth D, *et al:* The American College of Rheumatology criteria for classification and reporting of osteoarthritis of the hand. *Arthritis Rheum 1990;*33:1601–10.
7. Altman R, Alarcon G, Appelrouth D, *et al:* The American College of Rheumatology criteria for classification and reporting of osteoarthritis of the hip. *Arthritis Rheum 1991;*34:505–14.
8. Ratain JS, Hochberg MC: Clinical trials: A guide to understanding methodology and interpreting results. *Arthritis Rheum 1990;*33:131–9.
9. Bellamy N, Buchanan WW, Goldsmith CH, *et al:* Validation study of WOMAC: A health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol 1988;*15:1833–40.
10. Lequesne MG, Mery C, Samson M, *et al:* Indexes of severity for osteoarthritis of the hip and knee. *Scand J Rheumatol 1987;*(suppl 65)18:85–9.
11. Ayral X, Dougados M, Listrat V, *et al:* Chondroscopy: A new method for scoring chondropathy. *Semin Arthritis Rheum 1993;*22:289–97.
12. Buckland-Wright JC: Quantitative radiography of osteoarthritis. *Ann Rheum Dis 1994;*53:268–75.
13. Altman RD, Hochberg MC, Murphy WA Jr, Wolfe F, Lequesne M: Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cart 1995,*(suppl A)3:3–70.

14. Lequesne M: Quantitative measurements of joint space during progression of osteoarthritis: Chondrometry. In: Kuettner KE, Goldberg V, eds. *Osteoarthritic Disorders*. Rosemont: American Academy of Orthopaedic Surgeons, 1995:427–44.
15. Lynch JA, Buckland-Wright JC, Macfarlane DG: Precision of joint space width measurement in knee osteoarthritis from digital image analysis of high definition macroradiographs. *Osteoarthritis Cartilage 1993;*1:209–18.
16. Peterfy CG, van Dijke CF, Janzen DL, *et al:* Quantification of articular cartilage in the knee with pulsed saturation transfer subtraction and fat-suppressed MR imaging: Optimization and validation. *Radiology 1994;*192:485–91.

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