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Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the Osteoarthritis Research Society International

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Introduction

A Task Force of the Osteoarthritis Research Society International (OARSI) has previously published a set of guidelines for the conduct of clinical trials in osteoarthritis (OA) of the hip and knee[1]. Limited material available on clinical trials of OA of the hand[2–4] has prompted OARSI to establish a separate Task Force to elaborate guidelines encompassing special issues relating to hand OA. The Task Force was composed of academic physicians, clinical physicians and researchers in the pharmaceutical industry. Task Force expenses were supported by unrestricted grants provided by pharmaceutical company representatives (see the Acknowledgments section).

The Task Force elected to produce a set of guidelines that are based on the published medical literature supplemented by expert opinion. Small working groups dealt with specific aspects of trial design. The Task Force met in whole, or in part, on four occasions over a 4-year period between 2001 and 2005. Additional modifications of the guidelines were made through e-mail correspondence. The Board of Directors of the OARSI requested further refinement of the guidelines document and established a set of workshops at the OARSI World Congress on Osteoarthritis held in Chicago, in December 2004. Subsequent e-mail correspondence was required to address outstanding issues, and the final guidelines were submitted to *Osteoarthritis and Cartilage* for independent external review, and to the OARSI Board of Directors for approval, prior to publication.

As research methods for clinical trials in OA of the hand have not been as well developed as those for knee and hip OA[2–4], it is anticipated that the methodology for performing clinical trials of drugs for hand OA will evolve as more is learned. It should therefore be understood that the following recommendations will need to be modified as new information becomes available. Investigators, and representatives of regulatory and sponsoring agencies, need to be aware of the need for such changes; and new methodologies will need to be incorporated into the protocol design. The Task Force is of the opinion that changes in protocol design should be based on published data. The Task Force recommends that developers of new protocols should utilize credible and validated measures where available, for primary outcome assessments and should consider including, instruments and measurement techniques requiring initial or additional validation as additional secondary outcome measures.

The guidelines are recommendations, not rigid rules, for the conduct of clinical trials in OA of the hand. Many of the recommendations are supported by published clinical research. However, some recommendations have yet to be validated and are suggestions based on the best judgment and expert opinion of the Task Force at the time the guidelines were finalized. These guidelines have been constructed to build upon, and follow the pattern of, previously published guidelines[1].

Objectives for treatment of hand OA

Effective medications for OA may alter symptoms and/or modify structure and pathology (disease-modifying drugs for OA). Demonstration of these benefits will depend upon the trial design, outcome variables and measurement parameters selected. Trial design needs to take into account the mechanism and kinetics of action of the therapeutic intervention under consideration and the repertoire of responses expected.

The term *symptom-modifying drug* or agent will be appropriate for therapies directed at modifying symptoms. Pain or function will usually be the primary outcome variable. Factors that need to be considered in trial design include, but are not limited to, the pharmacodynamics of the drug, the time to clinical response, the duration of benefit after discontinuation of treatment, the route of administration, the effects on pain/function, the effects on inflammation, the effects on other symptoms and signs of the disease, and on the frequency and severity of adverse events.

A *structure (disease)-modifying drug* or agent may have effects on joint structure/function independent of any direct effect on symptoms. Studies of therapeutic interventions that are expected to modify the pathologic process of OA should measure outcome parameters that reflect an alteration in joint structure. Such treatments may prevent the development of OA, or change the course of OA, once it has developed. The latter category includes therapeutic agents that may have potential to stop progression, retard progression, or reverse existing OA changes. Symptomatic improvement may occur only after a prolonged period of administration. The Task Force has not developed a position on whether symptom response is needed to establish efficacy for a structure-modifying drug. It is clear, however, that a structure-modifying effect must result in perceptible clinical benefit within a relevant time point in the patient's lifespan. Whether related to symptoms, function or some other variable, the primary outcome measure should be clinically relevant to patients with hand OA.

Levels of clinical trials for hand OA

There are no special characteristics of trials for OA of the hand that require any alteration in the established sequence of phase 1, 2, 3 and postmarketing phase 4 trials[1].

Entering patients into hand OA trials

This section addresses the aspects of study design, including the protocol, admission criteria, and selection of the study population and the definition of what is to be studied.

For all nonhand OA-specific issues, the Task Force recommends following general guidelines for the conduct of clinical trials[5] and previously published OA-specific recommendations[1].

Baseline assessment should provide information on the joint sites to be studied, the aetiology (primary, secondary), the severity of symptoms, structural abnormalities in the joint, and concomitant therapy and comorbidity[2,3].

DEMOGRAPHICS

As a minimum, sociodemographic and clinical data collected at the time of enrollment into the study should include age (date of birth), gender, menopausal status in women[6,7], height, weight, and years of formal education. The patient's primary occupation should be noted and the identification of current or past activities involving intensive use of the hands (e.g., sports, gardening, playing specific musical instruments) is optional but desirable.

DIAGNOSIS

Criteria for the diagnosis of OA should be clearly stated. Patients should fulfill validated criteria for the classification

of OA, such as those published by the American College of Rheumatology (ACR)[8] (Table I). OA should be classified as primary or secondary. Study populations should be as homogenous as possible, with regard to the presence of primary or secondary OA. If patients with secondary OA, or exacerbating factors related to primary OA are included, the underlying condition should be specified, and should be the same in all patients (e.g., post-traumatic arthritis, calcium pyrophosphate deposition disease, hemochromatosis). It is suggested, that in studies of patients with idiopathic OA, patients with secondary OA of the study joint(s) should be excluded.

Much effort has been devoted to develop definitions of hand OA for use in epidemiologic and clinical studies[9–15]. Epidemiologic studies require explicit definitions of hand OA in order to separate cases from noncases[16]. These definitions may include individuals with and without clinical features of hand OA. Therapeutic studies, however, currently focus on patients with symptomatic hand OA. These may require case definitions that differ from those used in epidemiologic studies. There is no gold standard for case definition of hand OA at present, and this is an area requiring further research.

As with OA in other joint regions, it is difficult to divide hand OA into subsets. Trapeziometacarpal joint (first carpo-metacarpal or first CMC joint) OA may exist alone (estimated as approximately 20% of cases)[17], but most often occurs together with interphalangeal (IP) changes of OA[18]. Although protocols may study this group as a subset, evidence that first CMC OA represents a separate entity, rather than being part of the spectrum of hand OA remains controversial[19–21]. The exception could be the subset of the population with constitutional hypermobility[22]. However, the association between hand OA and hypermobility has recently been called into question[23].

It has been suggested that erosive IP OA may be a relatively uncommon, but separate, entity from nodal IP OA, which could be studied as a subgroup[24,25], should sufficient numbers be available. At present, however, there is no validated, uniformly agreed, and clear-cut definition of erosive IP OA for clinical trials; and this is an issue that could be explored through further research. Based on current evidence, the consensus is that erosive OA is a clinical subset of generalized OA[26] which falls within the definition of, and which is part of, the spectrum of hand OA as described in this document.

Table I
Algorithm for classification of OA of the hand, subcommittee on OA, American College Of Rheumatology Diagnostic And Therapeutic Criteria Committee

Clinical
1. Hand pain, aching, or stiffness for most days of prior month.
2. Hard tissue enlargement of >2 of 10 selected hand joints.*
3. Fewer than 3 swollen MCP joints.
4. Hard tissue enlargement of 2 or more DIP joints.
5. Deformity of 2 or more of 10 selected hand joints.*

OA present if items 1, 2, 3, 4 or items 1, 2, 3, 5 are present.

Sensitivity is 92% and specificity is 98%. Abbreviations: DIP = distal interphalangeal, PIP = proximal interphalangeal, MCP = metacarpo-phalangeal, CMC = carpo-metacarpal. Refer to: Altman *et al.*[8].

*Ten selected hand joints include bilateral 2nd and 3rd DIP joints, 2nd and 3rd PIP joints and first CMC joints.

STUDY JOINT AND DISEASE DURATION

Since hand OA is a polyarticular disease, protocols should specify the primary joint or region to be studied; i.e., both hands, the more symptomatic hand (usually the dominant hand), a single joint, a single ray, or a single row of joints. This is in contrast to the study of OA in other joints, where it is recommended that a single joint be prespecified as a target joint for evaluation.

Progression is joint specific[9,27]. Joint symptoms and signs in affected joints evolve independently; and changes in signs, symptoms, and imaging at one hand OA joint do not predict the course of OA in another joint. A patient selected for a clinical trial on the basis of a painful hand joint, may experience remission of symptoms in that joint within a few weeks or months. This may, or may not, coincide with development of symptoms in a previously asymptomatic finger joint. In general, symptoms of hand OA are transient, unpredictable, and irregular. The most severely affected joints on plain radiographs are not necessarily symptomatic, and are not consistently the most symptomatic[28–30]. As a consequence, advanced radiological changes are often associated with an absence of pain or functional impairment. However, there is some evidence that radiographic severity does correlate with the degree of deformity and bony enlargement[31,32]. The design of the protocol may focus on a set of hand joints or the most symptomatic joint, on both hands, or on the more symptomatic hand. In all cases, information on the status, and evolution during the study, of the other hand joints that are not being specifically investigated should be appropriately recorded.

Because of symptom variability, agents directed at symptom-modification may need to be administered for 4–6 weeks. Even though symptom response can often be determined in 2 weeks, it is appropriate to test durability and safety in longer trials. The Task Force recommends a study duration sufficient to permit the detection of a clinically-important statistically-significant, between-group, difference which may vary according to the type of intervention/drug tested. Nonsteroidal anti-inflammatory drugs (NSAIDs) are likely to be effective more rapidly than symptomatic slow-acting drugs in OA (SYSADOA). The minimum duration of study should be of the order of 4–6 weeks, although studies to evaluate the durability of the response should be longer in duration, possibly of the order of 6 months. For new drugs where insufficient safety data are available, long-term safety should be assessed in phase 3 trials of sufficient duration, possibly up to 12 months for systemic treatments. In trials directed at symptom-modification, follow-up after treatment has been stopped, and can be used to study the persistence of the therapeutic effect. The Task Force recommends a minimal duration of 1 year, and preferably 2–3 years, to optimize identification of structural changes. Validated imaging methodology will be needed, and can be explored through further research.

RADIOGRAPHS

Classically, the diagnosis of OA in epidemiologic studies has relied on the characteristic radiographic changes described by Kellgren and Lawrence in 1957[33] and illustrated in their Atlas of Standard Radiographs (Table II)[34].

The radiographic entry criteria should be appropriate for the specific study objective. For example, a cohort which includes patients with advanced radiographic changes might be appropriate in studies of a symptom-modifying drug, while a cohort limited to those with minimal radiographic

Table II
Grades of severity of OA in the small joints of the hands, Atlas of Standard Radiographs

Distal IP joints
- Grade 1: Normal joint except for one minimal osteophyte.
- Grade 2: Definite osteophytes at two points with minimal subchondral sclerosis and doubtful subchondral cysts, but good joint space and no deformity.
- Grade 3: Moderate osteophytes, some deformity of bone ends and narrowing of joint space.
- Grade 4: Large osteophytes and deformity of bone ends with loss of joint space, sclerosis and cysts.

Proximal IP joints
- Grade 1: Minimal osteophytosis at one point and possible cyst.
- Grade 2: Definite osteophytes at two points and possible narrowing of joint space at one point.
- Grade 3: Moderate osteophytes at many points, deformity of bone ends.
- Grade 4: Large osteophytes, marked narrowing of joint space, subchondral sclerosis and slight deformity.

First CMC joint
- Grade 1: Minimal osteophytosis and possible cyst formation.
- Grade 2: Definite osteophytes and possible cysts.
- Grade 3: Moderate osteophytes, narrowing of joint space and subchondral sclerosis and deformity of bone ends.
- Grade 4: Large osteophytes, severe sclerosis and narrowing of joint space.

Refer to: Kellgren *et al.*[33] Lane *et al.*[104]. [Reproduced from Silman, Hochberg (1993). Epidemiology of the Rheumatic Diseases. Oxford University Press, Oxford].

changes, would be more appropriate for studies of a structure-modifying drug intended to retard progression.

Potential limitations of the use of the Kellgren–Lawrence grading scheme have been noted[16,35,36]. These include overemphasis on the osteophyte as a marker of disease, and severity of disease, and difficulties in interpretation, leading to poor interobserver and intersite agreement. In an attempt to address some of these limitations of a global grading scale, several groups have developed radiographic grading schema which focuses on individual radiographic features of OA at specific joint groups; and reliable grading scales have now been published for the hand[27,37–39]. Using a published atlas, trained readers have been shown to have excellent intrareader and very good-to-excellent interreader reproducibility in measuring the presence and severity of OA of the hand[28,37–40]. Kessler *et al.*[29] have proposed a rapid hand scale based on a published atlas[38]. The method of Verbruggen and Veys[27,41] may permit a more detailed evaluation of disease progression.

The radiographic severity of OA in each patient should be semiquantified and documented using either aggregate radiographic criteria (e.g., Kellgren and Lawrence scale)[33,42] or grading of specific radiographic feaptures[27,38,39]. A current radiograph should be obtained upon entry to a structure-modifying trial. It is recommended that baseline radiographs for characterization of patients in trials of symptom-modifying drugs should be obtained within 3 months, and the interval between obtaining the radiograph and the start of the trial should not be longer than 12 months. The range of grades to be used for entry criteria should be prespecified in the protocol, in the expectation that with successful randomization, variations in grade among treatment and placebo (or control) groups should be comparable.

STUDY POPULATION

The patient population (e.g., community-based primary care, clinic-based secondary care or hospital-based tertiary care) should be defined in the protocol.

Examples of subjects who might be considered for inclusion or exclusion might be young ($<$45 years old), low-risk populations, or a variety of high-risk populations, as well as specific populations, such as those with isolated first CMC involvement.

For studies of symptomatic response, the level of symptoms at baseline should be of sufficient severity to permit detection of change (see Definition of severity below). Definite radiographic changes of OA are required and these should be graded using a validated scale and/or atlas.

For studies of structure-modifying therapeutic agents, special subpopulations of subjects, who are at high risk for development of OA, or rapidly progressive OA, may be advantageous. Selection criteria for structure-modifying trials should include at least two radiographically affected joints with a Kellgren and Lawrence radiographic grade $\geq$2[33]. Alternatively, investigators may utilize two joints at the J, S, E or R phase of the Verbruggen anatomical scoring system[27].

DEFINITION OF SEVERITY

In trials of symptom-modifying drugs minimum levels of symptom severity and symptom duration should be specified. Patients should have pain and tenderness in at least two IP or one CMC joint, or in a combination of IP and CMC joints. Pain should have been present for at least half of the days in the previous month and for at least 48 h prior to the screening visit. There should be pain in a joint that has been shown to have OA on a plain radiograph. Care should be taken to exclude subjects with referred pain (e.g., palmar tenosynovitis, carpal tunnel syndrome)[2,3].

There is no current consensus on what minimum level to set for pain severity on entry. It is proposed that on entry to a study there will be a hand pain score of at least 30–40 mm on a 100 mm-Visual Analog Scale (VAS) or at least 1 or 2 on a 5-point Likert (LK) Scale (0 = no pain; 4 = extreme pain) after withdrawal of analgesic/anti-inflammatory medications (see Administration of study medication/treatment).

There is also no current consensus on what minimum level to set for the severity of dysfunction on entry. It is proposed that for entry, into studies where function is a primary or co-primary outcome, patients should rate their disability as at least 25% of the scale length, e.g. $\geq$5 (out of a maximum of 30) points using the Functional Index for Hand Osteoarthritis (FIHOA)[44–47], which was the cut-off value shown to discriminate between symptomatic and nonsymptomatic hand OA patients[44], $\geq$9 (out of a maximum of 40) using the AUSCAN LK function subscale, or $\geq$225 F (out of maximum of 800) on the AUSCAN VA function subscale[48–54], as suggested by the authors.

In trials of structure-modifying drugs the study population should have a Kellgren and Lawrence radiographic grade of 2 or 3 (or equivalent) in the hand joint(s) to be studied[33], or alternatively, a radiographic S or J phase using the Verbruggen Scoring system (Table III)[27,41]. It is proposed that OA of at least two IP joints or one CMC joint be present on the screening examination[2,3].

There is no published data that allow one to make evidence-based recommendations, regarding the degree or extent of joint involvement required for disease prevention trials, in order to allow detection of new lesion development,

Table III
Summary of radiological outcomes and scales for structure-modification trials

Outcome	Recommended	Could be recommended may require further validation or precision on instrument	Could be interesting but requires validation
Radiographic case definition	Kellgren–Lawrence grading; Verbruggen anatomical scoring system	Use of a validated atlas	Magnetic Resonance Imaging
Identification of patients at risk of progression		Radionuclide bone scan	Computerized digital infrared thermal imaging
Radiographic assessment of OA progression	Kellgren–Lawrence grading; Kallman grading scale; Verbruggen anatomical scoring system and grading of progression; For all grading systems, each feature for each joint should be scored and analyzed	Global scoring: OA yes/no	Use of a published Atlas; Magnetic Resonance Imaging

in an acceptable period of time. In these circumstances the Task Force recommends that a low number (e.g., no more than one third of IP joints (i.e., six of 18)) should be involved at baseline, until this issue is clarified by further research. Because of the high frequency of involvement, the IP joints are appropriate sites for study in prevention trials. Each protocol should set a limit on the number of Kellgren–Lawrence grade 4 changes permitted at entry[2,3]. Alternatively, the limit could be based on the number of E or R phases in the Verbruggen Scoring system[27,41].

INCLUSIONS/EXCLUSIONS

Inclusion criteria should be clearly defined and should specify the population to be studied by age, gender, diagnostic criteria, joint with OA, types of and level of symptoms, and radiographic grade.

Exclusion criteria should also be clearly defined with regard to secondary OA, level of symptoms, radiographic grade, and comorbid diseases, as well as previous conditions of concern such as peptic ulcer disease, if a drug is perceived to have ulcerogenic potential. Exclusion of concomitant medications, pregnancy/contraception and recent treatment with intra-articular (IA) corticosteroids is also recommended. A minimum period of 1 month should elapse between the time of the IA injection of a depocorticosteroid and enrollment in a trial[55,56]. There should be a 6-month interval between the time of IA injection of a hyaluronate and enrollment in a trial. The necessity for, and appropriate duration of, a washout period (e.g., 3–6 months) for slow-acting symptom-modifying drugs should always be considered, and especially when the study drug itself is a slow-acting drug for symptom relief.

Additional exclusions recommended include significant injury to the affected joint within 6 months of trial enrollment; use of assistive devices such as a cane or crutch, concomitant rheumatic disease (e.g., inflammatory rheumatic disease, cutaneous psoriasis, polyarticular chondrocalcinosis, gout, carpal tunnel syndrome, palmar tenosynovitis, trigger finger, and fibromyalgia), or poor general health interfering with compliance or assessment[2,3].

OA HISTORY

The OA history is used to characterize the study population and should include the location and number of symptomatic OA joints, the presence of knee or hip OA, the duration of symptoms, the history of previous medications for OA, the use of splints, and any history of IA injections of depocorticosteroids or hyaluronan including the date of the most recent injection; and any history of previous hand surgery or other surgical procedures.

OTHER MEDICAL HISTORY

Other items of history at baseline that may be of value include a history of smoking, the patient's hormonal status in peri and postmenopausal women and any history of concomitant chronic disease, or medication, e.g., estrogens, anti-inflammatory drugs.

PHYSICAL EXAMINATION OF THE TARGET JOINTS

Baseline information about the target joint or joints helps to characterize the study population, and provides reference data for assessing how variables of interest have changed during the course of treatment. Evidence of inflammation and joint deformity should be noted. A complete standardized physical examination of hand joints should be performed at baseline, including: the description and number of symptomatic joints (e.g., painful joints), the description and number of tender joints, the description and number of Heberden/Bouchard nodes, the description and number of joints painful on pressure (on a diagram), and joints affected by lateral deviation, subluxation of the first thumb metacarpal, and if appropriate the number of inflamed joints as defined by redness, a recent exacerbation of pain, and soft peri/articular tissue swelling. This examination should be performed again at the end of the trial and may be considered for use as one of the secondary outcome measurements. The precision of these clinical measurements should be documented with data on observer reproducibility.

FUNCTION

Measurements of functional impairment can be used to identify the severity of disease in the study population. Functional impairment should be defined using a segregated, validated index (see Physical Function below).

GENERAL PHYSICAL EXAMINATION

A general physical examination should be performed at the onset of the study and again at the end of the study.

INFORMED CONSENT

Informed Consent should be obtained and documented in accordance with the Declaration of Helsinki[57] and studies should be approved by an appropriate institutional review board.

Conduct of the study

STUDY DESIGN

Studies should generally be controlled, using placebo or an active comparator where the comparator has been previously shown to be superior to placebo. They should be randomized and double blind (specifying the type of blinding procedure used), and parallel in design. Occasionally, crossover studies or other study designs may be appropriate; but it would be very unusual for unblinded or uncontrolled studies to be considered acceptable by regulatory agencies for purposes of registration. Studies may evaluate joints in both hands, or only in one hand; several joints, a single row of joints or just a single joint; depending on the research question being posed.

Studies may include an optional screening visit in addition to a baseline visit. Two pretrial visits allow the collection of more reliable baseline data (assuming absence of a washout period), and can increase assurance that patients fulfill entry criteria. They may also help to reduce noncompliance and may facilitate the collection of biological specimens. Consecutive patients enrolled for studies should be randomized for assignment, to treatment groups using validated randomization protocols.

At each visit, weight and vital signs (blood pressure, pulse) should be recorded and a report of adverse experiences obtained (see below).

In order to minimize variation in patient assessment, it is recommended that the same examiner should examine the same patient at each visit, preferably at the same time of day, throughout the duration of the trial.

STUDY OUTCOMES

Primary outcomes

Efficacy studies should specify a single, clearly defined, predetermined primary outcome variable or index. The choice of this outcome measure will depend upon the type of drug to be studied, the treatment effect of interest, and the specific objectives of the study.

Alternatively several primary outcome variables may be considered; but with this latter approach determination of significance will require appropriate adjustments for multiple analyses (see Statistical considerations below).

Secondary outcomes

The inclusion of one or more secondary outcome measures may strengthen the study design. Collection of information on secondary outcome variables should not interfere with collection of data on the primary outcome measure.

EXAMINER

The methods used for training the examiner and for blinding the examiner and the patients must be specified. Some studies may require both a blinded investigator to assess the patient for efficacy and adverse events, and an unblinded investigator to administer the test medication/treatment and monitor toxicity.

WASHOUT REQUIREMENTS

Symptom-modifying drugs/treatments

All studies of symptom-modifying treatments require discontinuation of previous analgesic and anti-inflammatory medications, including topical agents, prior to initiating treatment with the test drug/therapy, in order to permit the evaluation of unmodified severity of pain. The duration of the pretrial drug withdrawal should be determined by the time required for the clinical effect to disappear (e.g., 5 half-lives of the drug). During this washout period, subjects may need rescue analgesia (e.g., acetaminophen (paracetamol) up to 4 g/d). This must be discontinued sufficiently long before the clinical evaluation, for the interfering effects of the rescue drug to disappear.

Worsening of symptoms during the washout period, although not a necessary prerequisite for subject inclusion into the trial, should be documented. The possible merits of including a so-called ''flare design'' should be considered, although it is currently recognized that this is an issue that requires further research. In all studies of symptom-modifying treatments a specified level of symptoms is required for entry to the study.

There are a variety of ''nutriceuticals'' and alternative medicine products that are available and widely used by patients. The efficacy of some of these products has been tested in clinical trials. The use of such agents needs to be considered in the design of all OA treatment trials. Preferably their use should be excluded. Alternatively, if their use is to be continued it is recommended that patients should be taking a stable dose for a minimum of 3 months prior to entry to the study.

Structure-modifying drugs/treatments

A washout period may not be required in trials of structure-modifying drugs/treatments. If, however, the effect of the treatment on symptoms is to be tested, the use of a washout period should be considered. Because of possible effects of nutriceuticals and alternative products on disease progression, their use is precluded in trials of structure-modifying agents.

ADMINISTRATION OF STUDY MEDICATION/TREATMENT

Control agents may include placebo or active agents (e.g., analgesic or NSAID). Use of placebo may be influenced by ethical considerations or the requirements of regulatory agencies. The use of active comparators allows demonstration of equal or improved efficacy over existing therapies. However, they require prior validation as a reference treatment, and studies using active agents as comparators may require larger numbers of subjects, than placebo controlled trials, as they require the use of a noninferiority trial design.

Topical

Topical test medications should be dispensed in containers that are identical in appearance to those containing the comparator (active drug or placebo). The comparator should mimic the test medication in appearance, odor and local effects on the skin. Clear verbal and written instructions regarding use must be provided for patients. These

instructions must be contained in the Informed Consent. Compliance should be verified by weighing returned tubes, measuring amounts of returned liquid, or any other quantitative method more appropriate to the composition and presentation of the product. Placebo responses are particularly frequent with topical drug delivery, and this should be considered in protocol design and data interpretation. As topical therapy is predominantly a local form of treatment, joints to be treated and evaluated must be carefully predefined in all studies of topical agents.

Oral

Standard procedures for testing oral medications in hip and knee OA should be adopted in hand OA studies[1].

In studies of structure-modifying drugs concomitant medication (e.g., rescue analgesia and NSAIDs) should be dispensed in bottles and counted at each visit. Analgesic drugs with a short half-life should not be taken from the evening prior to the day of the assessment if pain is to be evaluated as the main outcome measure.

Parenteral medications

Parenteral medications should be formulated to appear identical to the comparator drug. If this is not possible, the parenteral medication should be dispensed and administered by a person other than the blinded investigator (i.e., by an unblinded investigator) and the injectable agent should be concealed from both the patient and the blinded evaluator.

IA medications

IA study medications should be formulated to appear identical to the comparator drug. If this is not possible, the medication should be injected by a physician other than the blinded investigator (i.e., by an unblinded investigator). The volume of the control to be injected should be equal to the volume of the test agent. The identity of the injected agent should be concealed from both the patient and the blinded evaluator. Placebo responses are particularly frequent following intra-articular injections[58], and this should be considered in protocol design and data interpretation.

Nonpharmacologic treatments (e.g., physical, devices, acupuncture, support programs, etc.)

A number of nonpharmacologic treatments have been proposed for the management of hand OA. Some have been tested in randomized controlled trials[2,4,59]. Approaches to blinding and the selection of appropriate control groups may differ from those used in trials of drugs; but outcome measurements are the same in trials of nonpharmacologic and pharmacologic treatments. The choice of controls, including sham interventions, may vary, depending upon the procedure to be tested (e.g., the control group will not be the same for the evaluation of a splint as it will be for a program of physical exercises). Cluster randomization of groups of patients, or therapists, may be appropriate when assessing certain nonpharmacologic treatments that involve group intervention.

COMPLIANCE

It is essential in studies of structure-modifying drugs, that strategies be employed to maximize and document patient compliance. For example, telephone contact might be maintained with patients at 4–8 week intervals. The method of communication and time spent with patients should be standardized as much as possible without jeopardizing the relationship with the patient.

SUBJECT RETENTION

Every effort should be exercised to maintain contact with patients, even when their participation in the study has had to be terminated earlier than planned (drop-outs). In all cases of premature discontinuation, a clinical assessment should be made (at least by a telephone call) and a radiographic examination should be routinely performed in structure-modification trials. For early termination of patients who are agreeable, a final visit at the original scheduled endpoint is advised and, in trials of structure-modification, this should include a radiographic examination.

PHARMACO-ECONOMIC ASPECTS

Sponsors should consider performing pharmacoeconomic analyses in all hand OA clinical trials[60]. In most hand OA trials, such analyses would form part of a battery of secondary outcomes requiring analysis. Depending on the type of health economic analysis (cost–effectiveness; cost–benefit; and cost–utility), the analysis could be based on relevant generic health-related quality of life and utility measures, general arthritis measures or OA-specific measures. The conduct of health economic evaluations may have important implications for trial design, including the sample size, outcome measurements, trial duration and data analysis.

USE OF CONCOMITANT MEDICATIONS

Symptom-modifying drugs/treatments

It is impractical to expect patients to participate in long-term trials without some recourse to rescue medication for pain. For long-term trials, the use of concomitant analgesic medication should be permitted on a limited basis. An example may be the use of acetaminophen (paracetamol) for escape analgesia (up to 4 g/d). However, any escape medication must be discontinued sufficiently long before clinical assessment, to allow its effects to have warn off at the time of assessment. Protocol design should routinely include a record of the consumption of analgesics, NSAIDs, and IA injections. Although the use of such information as an outcome measure in clinical trials of hand OA has not been validated, and requires further research, it is currently part of the battery of measurements used routinely in clinical trials, and should be included as a secondary outcome variable for efficacy. Short-term trials (i.e., less than 6 weeks) may not require escape analgesia. However, when necessary, acetaminophen could be allowed, and its consumption monitored.

IA depocorticosteroids should not be permitted within 1 month of entry to the clinical trial[55,56].

Structure-modifying drugs/treatments

Concomitant therapy may interfere with the evaluation of outcome measures and should ideally be excluded. However, in long-term studies, it is neither ethical nor practical to exclude all concomitant treatments. In all trials,

concomitant therapies (drugs or other interventions) that are likely to affect joint structure should be excluded, and rescue therapy should be permitted, standardized, carefully recorded and monitored. As noted above, subjects may use acetaminophen (paracetamol) for escape analgesia (up to 4 g/d), provided they discontinue acetaminophen, in sufficient time, prior to the study assessments.

The consumption of analgesics, NSAIDs, IA injections, topical agents, and nonpharmacologic interventions should be documented at each visit. There is, however, a need to develop methods to control the effects of these potentially confounding variables.

CONCOMITANT NONMEDICINAL THERAPY

Concomitant treatment with physical and/or occupational therapy should be either standardized or adjusted for the analysis, to ensure that the effects of exercise programs on disease progression do not bias the outcome of the study. Information on weight change (reduction or gain), introduction of, or changes in, the use of splints; and introduction of, or changes in, physical or occupational therapy during the study should be recorded, and prespecified, in the protocol.

LABORATORY TESTS

For most multicenter studies, routine laboratory tests (complete blood counts, urinalyses and serum chemistry determinations) should be performed in a central laboratory.

ADVERSE EVENTS

These should be carefully recorded and described and, if severe, immediately reported to regulatory authorities, in accordance with requirements for good clinical practice (GCP). All adverse events occurring during a trial should be followed up until complete resolution or stabilization has occurred. Safety considerations in hand OA trials should follow general recommendations for the conduct of clinical trials in patients with OA (see Ref. 1).

PROTOCOL VIOLATION

See in Ref. 1.

CASE REPORT FORMS AND SUPPLIES

See in Ref. 1.

Outcome measures for symptom-modifying trials

Instruments used to measure outcomes in clinical trials of OA should be valid, reliable, responsive to change and feasible. Clinical trials in hand OA should use validated instruments that have been used in previously published studies, thus permitting comparison of results across trials of different therapeutic interventions (Table IV). Consensus on three core set clinical measures for OA clinical trials was reached at the Outcome Measures in Rheumatology Clinical Trials (OMERACT) III Conference[61], and was subsequently ratified by the OARSI Task Force on Clinical Trials Guidelines[1]. The core set clinical measures specified in the original OMERACT and OARSI Task Force OA Clinical Trials Guidelines were: pain, physical function and patient global assessment; and for studies $\geq$1 year in duration: joint imaging.

Tools for the assessment of patient reported outcomes (PRO) fall into two basic acquisition categories, those which are doctor-administered, two of which, the Cochin Index[62,63] and the FIHOA[44–47], are illustrated in the Appendix to these Guidelines; and those which have been designed for patient self-administration, such as the Arthritis Impact Measurement Scales (AIMS, AIMS2)[64,65], the Australian/Canadian Hand Osteoarthritis Index (AUSCAN)[48–54], the European Quality of Life Measure (EuroQol)[66,67], Health Assessment Questionnaire (HAQ)[68], Health Utilities Index (HUI)[69,70], Nottingham Health Profile (NHP)[71,72] and Short Form 36 (SF-36)[73].

The tools can also be classified according to whether they are of generic quality of life measures such as the EuroQol[66,67], HUI 3[69,70], NHP[71,72] and SF-36[73]; general purpose arthritis measures such as the AIMS/AIMS2[64,65] and HAQ[68]; or disease-specific measures such as the AUSCAN[48–54], the Cochin Index[62,63], the FIHOA[44–47] and the Score for Assessment and quantification of Chronic Rheumatic Affections of the Hands (SACRAH), a self-administered instrument which was initially developed for use in both in RA and hand OA patients at the same time[74]. The responsiveness of this instrument remains to be studied.

The tools can also be distinguished according to whether they are, or not, copyrighted. Among hand OA-specific instruments, the AUSCAN is copyrighted, and the Cochin Index, the FIHOA and the SACRAH are not.

The following characteristics and features of hand OA-specific instruments have been reported in the peer reviewed literature. The instruments are presented in alphabetical order.

AUSCAN INDEX[48–54]

The patient-centered self-administered Australian/Canadian (AUSCAN) Index is a valid, responsive and feasible tri-dimensional (pain, stiffness, and function) index developed specifically for hand OA studies (Table V). The test–retest reliability (ICC = 0.70–0.90), internal consistency (Cronbach's alpha = 0.90–0.98), face, content and criterion validity (vs FIHOA, HAQ, Doyle Index, PGA, MDGA, grip strength, pinch grip and duration of morning stiffness) and responsiveness of the AUSCAN Index have been reported in a previous issue of this journal[48,49]. Comparative studies of the AUSCAN and a self-administered application of the FIHOA, which is not the validated form of the index, since the FIHOA has only been validated as a doctor-administered index, have been performed[49]. Since it was first developed, thirty-one alternate-language translations of the AUSCAN Index have been created, linguistically validated and are currently in use.

The original validation studies were conducted on 5-point LK and 100 mm visual analog (VA) scaled formats of the index, although an 11-point numerical rating scale (NRS) version is also in use. Like the Cochin Index, the AUSCAN Index has been validated in both OA and RA patients[54,63]. AUSCAN Index scores show comparable associations with grip strength and with radiographic severity of hand OA[52].

Post-validation experience with the AUSCAN Index in efficacy studies and licensing studies of new pharmaceutical products has confirmed the responsiveness of the AUSCAN Index, in phase 3 clinical trials[50,51].

COCHIN INDEX[62,63]

The Cochin hand functional disability scale is a unidimensional doctor-administered index, and a modification of the

Table IV
Summary of clinical outcomes and techniques for use in hand OA trials

Tool or instrument	Recommended	Could be recommended may require further validation or precision on instrument	Could be interesting but requires validation
Case definition	ACR criteria; Kellgren–Lawrence radiographic scale	Use of photographs; Patient self-definition for epidemiological studies	
Clinical assessment			
Pain assessment	Global pain on a VAS AUSCAN pain subscale		
Function assessment: Hand OA-specific	AUSCAN function subscale, Cochin Hand OA scale, FIHOA		
Nonhand OA-specific instruments (need to extract hand OA relevant items)	AIMS1/AIMS2 HAQ		
Patient's global assessment	Recommended but no validated formulation of a standard question		Standard question
Quality of Life			SF-36, SIP, EuroQol, NHP
Stiffness	Duration (min)AUSCAN stiffness subscale		
Joint examination: Deformity, Pain on pressure	Bouchard/Heberden nodes		Jeweler's ring, Doyle modification of the Ritchie Index
Performance-based measure		Backman Test	
Aesthetic damage assessment			To be determined
Escape medication	NSAIDs and analgesics consumption although not validated must be monitored and recorded		
Response criteria			Certainly useful. To be determined and validated

index developed by Duruöz *et al.*[62] for use in rheumatoid arthritis hand studies. The index has been revalidated in hand OA patients, and the validity, responsiveness and feasibility of the Cochin Index have been reported in a previous issue of *Osteoarthritis and Cartilage*[63]. Index scores correlate with FIHOA scores (Spearman coefficient, $r = 0.87$), and pain severity scores. The Cochin Index contains 18 questions concerning daily living activities, rated on a 6-point scale (from 0 = yes possible without difficulty to 5 = impossible to do) (Table VI). The total score ranges from 0 to 90. A factor analysis demonstrated that four factors accounted for 65% of the total variance. The first two factors related to activities requiring grip strength and activities requiring dexterity and precision. The mean time for administration was reported to be around 3 min in RA patients[62]. A comparative analysis of various instruments was performed to identify which of these instruments discriminated best between patients who had improved and patients who had deteriorated. The four best instruments were, by statistical rank: the global handicap rated on a VAS, the Cochin Functional index, the global pain on a VAS and the FIHOA. The Cochin Index exhibited a greater Standardized Response Mean (SRM), compared to that of the FIHOA in the 19 patients who deteriorated (−0.75 vs −0.38), but in patients who had improved, the FIHOA showed a better SRM (0.42 vs 0.30) than the Cochin Index[63]. The Cochin Index is available in French and English validated formats.

FIHOA[44–47]

The FIHOA[44–47] is a unidimensional doctor-administered index and was the first index validated for use in patients with hand OA (Table VII). The FIHOA is a valid, responsive and feasible measure of physical disability in hand OA patients[44,45]. The FIHOA contains 10 questions and scores responses on 4-point verbal rating scales to avoid any "centralization" of the answers (the total score ranges from 0 to 30) (Table VII).

Data on its responsiveness have been published in a previous issue of this journal[45] and have shown that it is a little less responsive than global pain assessment on a VAS in a 6-month trial performed in painful hand OA patients (SRM = 0.58 vs 0.87). A minimum score of 4–5 (range 0–30) seems to discriminate appropriately between symptomatic and nonsymptomatic hand OA patients[44]. It is easy to perform and not time consuming (2.5 min in average for completion). Since it was first introduced, seven linguistically valid alternate-language translations of the FIHOA have been created, and are currently in use. The FIHOA score shows comparable associations with grip strength and with radiographic severity of hand OA[46]. Post-validation experience with the FIHOA Index in efficacy studies has confirmed the responsiveness of the FIHOA Index in clinical trials[47].

Regardless of the PRO instrument selected, measurements should be recorded at baseline and serially at appropriate intervals. For studies of drugs designed to improve symptoms, the primary outcome variable is usually joint pain reported by the patient. Measurement should be serially recorded at appropriate intervals, at least monthly. The exact schedule is dependent on the target joint selected, the study design and the research objective.

In a systematic search and critical review of measures of disability for use in hand OA, which included the AIMS2,

Table V
*Australian/Canadian (AUSCAN) hand OA index: subscale structure and item content list (Adapted with permission from AUSCAN User Guide II)**

Pain subscale
1. Rest
2. Gripping
3. Lifting
4. Turning
5. Squeezing

Stiffness subscale
6. First wakening

Physical function subscale
7. Turning taps/faucets
8. Turning a round doorknob or handle
9. Doing up buttons
10. Fastening jewelry
11. Opening a new jar
12. Carrying a full pot
13. Peeling vegetables/fruits
14. Picking up large heavy objects
15. Wringing out wash cloths

- The AUSCAN Index is patient self-administered and available in three scaling formats: 5-point LK, 100 mm VA, and 11-point NRS
- AUSCAN website at www.auscan.org.
- AUSCAN User Guide available
- Alternate-language translations currently available and in use: Australia, Austria, Belgium (French, Flemish), Canada (English, French), Czech, Denmark, Finland, France, Germany, Hungary, Iceland, Israel, Italy, Lebanon, The Netherlands, New Zealand, Norway, Poland, Romania, Russia, Slovakia, South Africa (English, Afrikaans), Spain, Sweden, Turkey, United Kingdom and USA (English, Spanish).

Refer to: Bellamy *et al.*[46,47].

Table VI
*The Cochin hand functional disability scale**

In the kitchen
1. Can you hold a bowl?
2. Can you seize a full bottle and raise it?
3. Can you hold a plate full of food?
4. Can you pour liquid from a bottle into a glass?
5. Can you unscrew the lid from a jar opened before?
6. Can you cut meat with a knife?
7. Can you prick things well with a fork?
8. Can you peel fruit?

Dressing
9. Can you button your shirt?
10. Can you open and close a zipper?

Hygiene
11. Can you squeeze a new tube of toothpaste?
12. Can you hold a toothbrush efficiently?

At the office
13. Can you write a short sentence with an ordinary pen?
14. Can you write a letter with an ordinary pen?

Other
15. Can you turn a round door knob?
16. Can you cut a piece of paper with scissors?
17. Can you pick up coins from a table top?
18. Can you turn a key in a lock?

Scoring System: 0 = yes without difficulty; 1 = yes with a little difficulty; 2 = yes with some difficulty; 3 = yes with much difficulty; 4 = nearly impossible to do; 5 = impossible to do. Refer to: Poiraudeau *et al.*[63].

Table VII
The dreiser FIHOA – English version validated with the help of Boulos Haraoui

1. Are you able to turn a key in a lock?
2. Are you able to cut meat with a knife?
3. Are you able to cut cloth or paper with a pair of scissors?
4. Are you able to lift a full bottle with the hand?
5. Are you able to clench your fist?
6. Are you able to tie a knot?
7. *For women* – Are you able to sew? *For men* – Are you able to use a screwdriver?
8. Are you able to fasten buttons?
9. Are you able to write for a long period of time?
10. Would you accept a handshake without reluctance?

Scoring system: 0 = possible without difficulty; 1 = possible with slight difficulty; 2 = possible with important difficulty; 3 = impossible. Refer to: Dreiser *et al.*[44,45].

AUSCAN, Cochin Index, FIHOA and HAQ, Dziedzic *et al.*[75], using quality assessment criteria, noted that the AIMS2 and the AUSCAN Index were more highly rated than the FIHOA, Cochin and HAQ.

The Task Force came to the conclusion that at the present time no one instrument can be recommended over another and that the choice of instrument(s) for a specific project will depend on the study design and the research questions being asked. Further comparisons of the instruments within the same hand OA trials are needed.

PAIN

The measurement of pain is a core set outcome measure. Pain should be measured using a single item or multi-item 100 mm VA, 11-point NRS or LK scale[76]. Pain is usually measured on one or more rating scales which grade perceived pain severity in one or more of the several situations, e.g., pain at rest, pain on motion, or global pain during a specified recall period, which is often 24 h or 48 h[76]. The OARSI Hand Osteoarthritis Task Force recommends using a single item global pain VAS for the selection of patients for study inclusion, and for subsequent pain assessment during the course of the study, either the pain subscale of the AUSCAN Index[48–54] or a single item global pain scale. To assess global pain, a standard question could be asked e.g.: "How much pain in your hand did you experience during the last 48 hours?"

Since pain may vary dramatically over time and "jump" from a joint to another, pain assessment should be performed over defined periods of time. This can be achieved by the use of personal daily diaries where patients are asked to record the amount of pain in the target hand, or by using the "weekly self-assessment of painful joints" that has previously been proposed but not yet fully validated[77].

While useful in the measurement of generalized arthritis, the HAQ pain subscale[68], or the pain subscales of the AIMS[64] or AIMS2[65] are of qualified value for phase 3 hand OA clinical trials, since they do not specifically assess pain attributable to the hand joints. It is suggested that in order to use generalized OA measures for this purpose (HAQ, AIMS, AIMS2), questions relating to pain specifically referable to hand joint OA may need to be selected out from the instrument[64,65,68].

PHYSICAL FUNCTION

The measurement of physical function is a core set outcome measure. Physical function/disability is usually

measured on a rating scale (LK, NRS, and VAS) which grades the perceived severity or degree of disability in one or more activities of daily living (e.g., turning taps/faucets on, opening a new jar)[78]. The majority of previous hand OA studies have not used standardized health status measures of physical function[59]. Function should be measured using the AUSCAN Index[48–54], the Cochin Index[62,63] or the FIHOA Index[44–47].

PATIENT ASSESSMENT OF GLOBAL STATUS

The patient's assessment of his/her global status should be measured using a LK, NR or VA scale. There is currently no validated standard question, and no standard response format for conducting this measure[4,59,78]. The optimal method by which this should be measured is not well established. However, a standard question could be asked e.g., ''Considering all the ways your hand OA affects you, how have you been during the last 48 hours?'' Despite the limitation of the method, patient global assessment is a core set outcome measure. The proposed formulation could be validated through further studies.

PHYSICIAN ASSESSMENT OF GLOBAL STATUS

A measure of the physician assessment of global status may be required in some cases. There is no generally accepted method for measurement of this variable. A standard question such as ''Considering all the information you have, how is the patient's hand OA today?'' could be used, responses being recorded on a VA, NRS or LK scale. Physician global assessment is not a core set outcome measurement.

QUALITY OF LIFE SCALES

Measurement, at appropriate intervals, of health-related quality of life and utility is recommended; although, these are not currently core set outcome measures[1,61,79]. They not only allow measurement of the patient's quality of life or the utility of their health status, but also facilitate pharmaco-economic analyses and cross-disease comparisons of outcome. To date, there is no experience with these instruments in OA hand trials. Examples of health-related quality of life instruments include the SF-36[73], Sickness Impact Profile (SIP)[80], NHP[71,72] and EuroQol[66,67]. Utility can be measured using the EuroQol or HUI[66,67,69,70].

JOINT EXAMINATION

The clinical examination provides an opportunity to detect, tenderness, range of movement, bony enlargement and inflammation. Previous hand OA studies have included measurement of tenderness by palpation, pressure (see below) or by dolorimeter; measurement of joint swelling using jeweler's rings; quantitation of the number of inflamed Heberden's nodes and/or measurement of joint range of motion[4,59].

Pain

The Doyle modification of the Ritchie Index has not been specifically validated for hand OA clinical trials[2,3], but its basic clinimetric properties in OA have been previously published[81]. Dolorimeter assessments do not appear to be reliable[59].

Mobility

Range of motion has shown inconsistent intrarater reliability. It is possible to improve consistency of examination if the examiner undergoes training.

Deformity

Measurements of deformity may involve assessment of bony enlargement or angular deviation. In OA, bony enlargements such as Heberden's nodes, Bouchard's nodes or knobbly deformity at the first CMC need to be recorded. Jeweler's rings may be used to quantify joint circumference. However, training sessions may be needed to establish reliable measurements[82]. Although not a core set outcome measure, the presence of deformity should be recorded on the screening visit and at endpoint in long-term clinical trials assessing both structure and symptom-modification. This can be conducted as part of the physical examination proposed in General physical examination, and performed at baseline and termination visits.

Inflammation

For both the description of the study population and the assessment of changes following treatment it may be useful to record the number and location of inflamed joints, as defined by redness and soft periarticular or articular tissue swelling. This should be done at the screening visit and, as a minimum, at the endpoint of the study.

PERFORMANCE-BASED MEASURES

Performance-based measures, which include such techniques as grip strength have been studied[83], to some extent, but how these measures vary over time is unknown[59,82,83]. The Backman's hand function test has been developed to explore some aspects of both hand function and performance, such as grip strength and pinch grip; and has been used in a clinical trial[59,84]. It has been used by physical and occupational therapists to measure improvement in functional capacity, but its responsiveness has not been studied in hand OA. Its use requires specific devices, trained investigators, and it is time consuming. Performance-based measures are not currently core set outcome measures.

STIFFNESS

The duration and severity of joint stiffness can be assessed, but these are also not core set measures.

There is currently no standard wording for questions relating to the duration of joint stiffness in hand OA. When duration of stiffness is used as an outcome measurement, a standard question such as ''What is the duration of stiffness in your finger joints in the morning?'' (expressed in minutes) is recommended. Based on experience in hip/knee OA, patients need to have a clear understanding of reference points for the onset (''on first wakening'' vs ''on getting out of bed'') and the offset (''starts to ease off'' vs ''when fingers are as limber as they will be for the rest of the day'') of joint stiffness in order to estimate its duration. When the severity of stiffness is to be measured in clinical trials, the AUSCAN Index stiffness subscale may be used[48–54].

AESTHETIC DAMAGE ASSESSMENT

The Task Force recognized the potential importance of a measure of aesthetic damage. The extent to which

deformities in affected joints are matters of concern for men, and especially for women with hand OA, has not been systematically assessed or quantified. The task force was unaware of any instrument currently available that has the capacity to make such measurements and the impact of aesthetic damage is not a core set outcome measure. A standardized question, which has yet to be developed, could help to address this issue, but needs to be explored through further studies.

"FLARES"

The "number of flares" and the definition of "flares" lack precise description. There is no validated tool currently available to perform this measurement. It is suggested therefore that "flares" should not be used at this time as an outcome measure (however, see "flare design" as an inclusion criterion above). This issue could be explored through further studies.

ESCAPE MEDICATION

Analgesic and NSAID consumption should be carefully recorded at baseline and at each visit. While escape medication usage has not been validated as an outcome for hand OA clinical trials, it certainly provides important information, and should be recorded in clinical trials.

RESPONSE CRITERIA

There are no definitions of minimum clinically important responses for any of the above measures in OA of the hand. As there is no published data which can be used to set predetermined threshold values for improvement, as has been recommended for hip and knee OA studies[85,86], the Task Force cannot currently recommend the use of any specific individualized response criteria for adjudicating responses to treatment in hand OA studies[85,86]. Further research is needed to develop such responder criteria for hand OA studies. This objective could be approached, by incorporating response-based research questions in future clinical trial protocols.

Outcome measures for structure-modifying trials

For studies of potential structure-modifying drugs, the primary outcome variable should be a measure of joint morphology; such as an imaging modality. Clinical follow-up of patients participating in trials of structure-modifying drugs should be at 3 intervals of 3 months or less.

JOINT IMAGING

The plain radiograph remains the most available and standardized method for the evaluation of hand OA[2,3,37,40,41]. The separation of nonerosive from erosive OA remains controversial[87]. It is anticipated, that as magnetic resonance imaging (MRI) becomes more readily available and more affordable, measurements currently undertaken with joint radiographs will be performed by MRI[88,89]. However, further prospective studies of MRI are needed before MRI can replace the radiograph, for clinical trials of structure-modification of the hand. Patient selection for structure-modifying trials may be informed by the radionuclide bone scan, since localization of the nuclide to particular bony sites may predict future progression of disease[90,91]. However, radionuclide bone scans are not readily available at all investigator sites and the examination is time consuming and expensive. The Task Force does not recommend the routine use of radionuclide bone scans to select patients at risk of radiographic progression, for structure-modification trials.

The computerized, digital, infrared, thermal imaging proposed by Kraus *et al.*[92] may, in future, help to identify patients at risk of rapid progression of structural changes of hand OA at a stage when radiographic changes are absent or minimal. While the technique may have some value in the selection of patients at risk of radiographic progression, the method requires further validation in longitudinal studies[92].

Radiographic technique

For symptom-modifying trials, where a radiograph is obtained for diagnostic purposes, a single postero-anterior radiograph of both hands with the hands parallel on the same cassette is acceptable. Quantitative microfocal radiography may offer advantages over routine radiography, but is not readily available[93]. Digitized images do not provide additional information for interpretation[94]. Computed tomographic images do provide better definition of changes, but the techniques have not been extensively tested[95].

For structure-modifying trials, a postero-anterior radiograph of each hand on separate cassettes should be obtained. It is recommended that the radiographs be obtained at the point of enrollment in the study and again at yearly intervals. A hand map is recommended for reproducibility of position. In order to assure a standardized technique, data on the initial radiograph should include type of radiographic film, type of radiographic cassette, kilovolts, milliseconds, and milliamperage. These should be identical in subsequent studies. Unless there is a special reason, the first CMC joint does not need to be imaged separately[96].

It is anticipated that in many future trials, films (whether they have been taken as plain or digitized radiographs) will be digitalized and loaded on CDs or DVDs for reading and analysis in a central center. Digitalized films will be read on a computer screen, rather than on a light box, and this will allow magnification of the images.

Readers

The trial design should specify the number of radiographs and any special training required for radiograph readers. Although a single, well-qualified reader may suffice[97], it is of note that one previous study compared different readers and recommended three for internal consistency[98]. It has, however, not been proven that using 2 or 3 readers is superior to using one single trained reader. A recent study performed in hip OA, which compared two readers vs one, did not observe any advantage in using more than one trained reader; and recommended that the "best" reader be selected, among several, before starting the trial[99]. The use of a single reader is likely to improve longitudinal sensitivity to change; and so help to minimize the number of patients needed to be included. Training sessions usually improve the consistency of the readings. The reader may be any trained specialist. However, since no radiographic scoring method has been extensively validated in hand OA, and since little is known with respect to how these grading methods capture changes over time, the use of 2 readers could be considered[98]. When there is more than one reader, the trial design needs to specify how differences in readings will be adjudicated and how data will be analyzed (i.e., each reader's scores, mean of the scores

of both readers, etc.). Evidence-based recommendations, regarding the number of readers that is optimal must await the results of further research. The goal is for radiographs to be read with high levels of inter-reader and intrareader precision. Protocols should include specification of the precision of the method employed (i.e., inter-reader, cross-sectional and longitudinal intrareader reproducibility and sensitivity to change should be specified).

For all trials, the radiographs should be masked for the patient name and the radiograph should be identified by a code. For both symptom and structure- modifying trials, the prestudy films should be evaluated, prior to entry into the study, to confirm the diagnosis.

For structure-modifying trials, all films from a single patient should be evaluated at the same time after the final films have been obtained. For most studies, the radiographs of each patient should be masked and labeled in random order; so that the reader is blinded as to the sequence and the date the radiograph was obtained, as well as to the treatment given. If the protocol allows the reader to be aware of the time sequence, this potential source of bias should be identified in the protocol, and an appropriate explanation and justification provided. It can, however, be anticipated that any potential bias that might result from the reader's knowledge of the time sequence of the films will not affect conclusions in a double-blind experiment, where the reader has been blinded to the nature of the treatment arms. For intrareader reproducibility, a prespecified number of pairs of baseline and endpoint radiographs should be re-read (test−retest) at each session and between sessions. Re-reading of radiographs allows calculation of the intrareader cross-sectional and longitudinal variability[99]. If there is more than one reader, inter-reader variability should also be calculated using the same sample pairs of radiographs.

Joints examined

The protocol should specify which joints are to be radiographically evaluated. In some studies this may include up to 16 joints (one hand) or 32 joints (both hands), including MCPs, first CMC and scapho-trapezial joints.

All trials should include a radiograph of all the distal interphalangeal (DIPs), proximal interphalangeal (PIPs) joints, and the first CMC (or trapeziometacarpal) joints. However, some protocols may be designed not to evaluate all DIP and PIP joints, while others may elect to include all DIP, PIP, first IP joint, and the metacarpo-phalangeal (MCP) joints.

Anatomic changes examined

All trials need to record changes in the above joints that reflect joint space narrowing and presence of osteophytes[33,91,98,100,101]. Additional measurements to be included are erosions, subchondral sclerosis, subchondral cysts and deformity[38]. The protocol should define each of these features and how they are to be recorded. Although osteophytes or joint space narrowing might be more sensitive to change in the evaluation of progression, measurement of all radiographic features is recommended at this time[99,102].

Measurement of the above radiographic features may be performed using a global scale[27,38,41,101,103], by a summation score, or by the individual features (Tables VIII and IX)[2,27,28,41,91,104]. These features may be recorded as present/absent or graded using ordinal, interval or ratio scales. A LK scale of 0−3 (0 = absent; 1 = mild; 2 = moderate; 3 = severe) may be used. Atlases have been published to improve standardization of ratings of individual radiographic features[28,37].

Table VIII
Numerical and anatomical radiographic scoring system for the assessment of hand OA by Verbruggen. Points attributed to changes in osteoarthritic joints

Osteophytes	Appearance/ disappearance	+1.0/−1.0
	Increase/decrease in size	+0.5/−0.5
Joint space	Narrowing/widening	+1.0/−1.0
Subchondral cysts	Appearance/ disappearance	+1.0/−1.0
	Increase/decrease in size	+0.5/−0.5

Refer to: Verbruggen *et al.*[27,41,101].

Different published methods offer advantages that may be applicable for a particular trial design. A summation score may be adequate for disease classification and for population surveys. In addition, for structure-modifying trials, the Task Force is of the opinion that none of the presently available global scales or summation scores has been adequately validated or compared with others. Although the individual features have also not been adequately validated in prospective trials, the Task Force recommends that individual radiographic features in each of the selected joints should be recorded for each joint. Alternative methods using factor analysis to determine optimal combinations and weightings of various radiographic features, can be considered, but these require validation in hand OA studies. If summation scores are to be used, they should be confined to specific features (e.g., osteophytes). In particular, investigators should avoid combining the ratings of osteophytes and joint space narrowing, unless the proposed method has been previously validated. In all studies the primary radiographic outcome measurement to be used must be prespecified.

Table IX
Radiographic scoring scale for hand OA proposed by Kallman. Rating methods used in scales for grading individual features of OA of the hand

Feature	Grade
Osteophytes	0 = none 1 = small (definite) osteophyte(s) 2 = moderate osteophyte(s) 3 = large osteophyte(s)
Joint space narrowing*	0 = none 1 = definitely narrowed 2 = severely narrowed 3 = joint fusion at least 1 point
Subchondral sclerosis	0 = absent 1 = present
Subchondral cysts	0 = absent 1 = present
Lateral deformity†	0 = absent 1 = present
Collapse of central joint cortical bone	0 = absent 1 = present

Refer to: Kallman *et al.*[38,99].

*Scores are based on the amount of narrowing between bone and plates, not on osteophyte bridging.

†Defined as malalignment of at least 15 degrees.

MAGNETIC RESONANCE IMAGING (MRI)

MRI is uniquely capable of visualizing all components of the joint simultaneously, and therefore offers an opportunity to assess the joint as an organ. MRI is capable of quantifying a number of morphological and compositional parameters of articular tissues relevant to OA. Recently developed techniques for knee OA, for noninvasively quantifying cartilage volume, thickness and water content, particularly in early disease, show promise as potential outcome measures for future therapeutic studies. There have been no cross-sectional or longitudinal studies of MRI in hand OA. The use of MRI for hand OA studies requires further research.

OTHER IMAGING MODALITIES

Computed Tomography, ultrasonography and scintigraphy have not been adequately validated and cannot currently be recommended for use in long-term hand OA studies.

Radionuclide bone scanning may assist in identifying patients at increased risk of disease progression. Although there is some evidence that finger joints showing increased localization of the radionuclide are more prone toward progression[91], the method cannot currently be routinely recommended.

MOLECULAR AND GENETIC MARKERS

Disease ''markers'' have been sought to provide information that would be useful for diagnosis, for the assessment of the patho-physiological ''activity'' of the disease and for assessment of prognosis. Such biological markers can include clinical features, imaging modalities, genes,that predispose to the initiation or progression of disease and pathological features (e. g., histological, immunological, biochemical or microbiological).

A variety of different biochemical markers of cartilage, bone and synovial tissue metabolism have been investigated in synovial fluid, blood or urine of patients with OA[105–107]. The majority of such research, however, has focused on knee or hip rather than hand OA[108]. Certain markers measured in knee synovial fluid, such as chondroitin sulphate epitopes, differ according to presence or absence of hand OA, suggesting constitutional differences, irrespective of which joint is sampled[109]. A marker (Col2-3/4Cshort, a marker of cartilage catabolism) has been shown to be increased in a population of hand OA patients compared to controls, without any difference between nodal and erosive subsets[107]. Nevertheless any marker for hand OA, that is to prove clinically useful, would need to be estimated in blood or urine, rather than synovial fluid. Although abnormalities in serum measures (e.g., immunoglobulin levels, rheumatoid factor seropositivity) have been reported in subjects with hand OA, these changes are nonspecific[110]. Future research work is therefore required to identify biochemical markers that are more informative than existing clinical and imaging markers with respect to early diagnosis, disease activity and prognosis.

The importance of genetic influence on the development of Heberden's nodes and hand OA is well recognized, the variance attributable to heritability being estimated at $>60\%$[111]. Such strong heritability clearly emphasizes a need for genetic linkage and association studies, and many such studies are currently underway. Recent studies have revealed linkages between loci on chromosome 2q with both multiple Heberden's nodes[112] and radiographic hand OA[113], although the genes involved have yet to be identified. Specific genetic associations with hand OA have, however, been reported, for polymorphisms of the IGF-1 gene[114] and aggrecan genes[115] in Dutch and American populations respectively, and with the vitamin D receptor[116] and estrogen receptor[117] genes in Japanese subjects. Although such work is at an early stage, it is hoped, that in the near future it will result in the identification of highly informative genetic markers for the development and outcome of hand OA.

Statistical considerations

General statistical guidelines and recommendations for OA studies were formulated by an earlier OARSI Task force and published in a special report in *Osteoarthritis and Cartilage* in 1996[1]. These recommendations remain valid and are applicable to studies of hand OA. The Task Force on hand OA has, however, developed recommendations for how researchers could analyze information from radiographs, while recognizing that no single feature is consistently associated with disease progression. The following are guidelines for the statistical evaluation of outcomes, with emphasis on how to evaluate more than one primary outcome variable.

CHOICE OF OUTCOME VARIABLES

Elsewhere in this document the Task Force has recommended that trials should include evaluation of DIP, PIP and first CMC joints and that individual radiographic features of joints should be assessed for change.These include changes in joint space, the presence and severity of erosions, the presence of osteophytes and possibly some other radiographic features such as spurs, sclerosis and deformities

However, individual radiographic features are scored and quantified, the prespecified primary radiographic outcome, which is subjected to statistical analysis, should be directly related to the research objectives of the study, and should take into consideration the polyarticular presentation of hand OA. If the researcher or sponsor of the research hopes to claim that a treatment is structure-modifying as assessed by changes in joint width, spurs and erosions, then a combined primary outcome variable might be appropriate. However, the pharmacological mechanism of action of the potentially structure-modifying agent also needs to be considered. If the primary effect is expected to be confined to retardation of joint space narrowing or erosive disease, then assessment of a single feature such as joint space width would be a more appropriate primary outcome measure.

The intended claims may, however, require evaluation of more than a single prespecified primary outcome measure. If, for example, the sponsor or researcher wishes to demonstrate symptom-modification as well as structure-modification of the agent to be studied it may be appropriate to have two prespecified ''co-primary'' outcomes (one for structure-modification, and one for symptom-modification) and the power calculation for the number of subjects required will need to take both the primary endpoints into consideration. If the objective is to investigate whether the treatment is also symptom-modifying, then patients included for study will need to be experiencing at least a moderate amount of the symptom in question at the point of enrollment.

The Task Force recommends that the radiographic features chosen to measure change be individually scored in a standardized, manner in all study patients, and all joints

prespecified for assessment according to protocol – at baseline and at all study follow-up visits. The aim is to capture change over the duration of the trial, recognizing the diverse presentation of hand OA, and that different joints and joint features may be variably affected at baseline, and as the trial progresses. One patient may present with involvement of several DIPs, but only with pain in the first CMC joint. Another patient may present with six affected DIP and PIP joints, only 2 of which are painful; and at the end of the study, 3 of the same joints may remain affected, with 4 others affected with pain. Since standardized measurements are obtained from all subjects' radiographs, both the primary and secondary radiographic outcome measurement scores can be calculated for each patient. How multiple features scored at multiple and diverse joints are to be weighted, combined and quantified for analysis as a primary outcome, should be made explicit in the protocol. If radiographic scales are used, the number of joints assessed, and the way features are summated, should be prespecified in the protocol.

As previously mentioned, there may be more than one primary outcome reflecting the efficacy claims for the drug under investigation. If the chosen primary outcome has not been previously validated, then a preliminary study will be required to establish the validity, responsiveness and feasibility of the outcome measure.

The Task Force recommends that the following steps be used to analyze co-primary outcomes:

First, for each of the co-primary outcomes, values of the test statistic more extreme than the 2-sided critical value (for example, more extreme than ± 1.96 for normally distributed outcomes) provides nominal, single outcome evidence to reject a null hypothesis, at the 2-sided 0.05 significance level. Some analytic methods used to compare single outcomes among treatments have previously been outlined.

Secondly, since there are co-primary outcomes, an adjustment in the observed *P*-values may be necessary to establish the statistical significance of outcomes. We recommend using Hochberg's correction for multiple comparisons[118]. This method is easily implemented. For example, suppose there are three co-primary outcomes (radiographic change, change in pain, patient global assessment of change). Then, (1) if all three *P*-values are ≤ 0.05, then all three hypotheses are significant, (2) if one *P*-value exceeds 0.05, then either (or both) of the remaining *P*-values must be ≤ 0.025 to achieve significance, (3) if two *P*-values exceed 0.05, then the remaining *p*-value must be $\leq .0167$ for this outcome to achieve statistical significance. If none of the above 3 scenarios hold, then none of the three co-primary hypotheses is statistically significant.

For multicenter trials of symptom-modifying treatments, block randomization may be preferable to simple randomization to ensure that numbers of patients receiving active treatment and control therapy are comparable as patient recruitment is likely to continue over a long time. Restricted randomization with stratification to ensure a good balance of key baseline characteristics of patients in the active treatment and control groups may also be required in some instances. Secondary analyses on subsets of patients deliberately stratified for randomization between treatment groups (e.g patients presenting with OA in the first CMC as the only symptomatic joint) may be of particular interest, but intention to undertake such subset analyses should always be clearly prespecified in the protocol.

The Task Force recommends that power calculations for estimation of sample size, for each protocol must be based on predefined improvements in a carefully defined primary efficacy variable that is clinically relevant as well as statistically significant Meaningful definitions of minimum clinically important differences in two groups of patients exposed to different interventions, will depend on a number of factors relating to patient characteristics, features of disease, the nature of the intervention and the primary outcome measures selected. Unfortunately it is not currently possible to make firm recommendations with regard to minimum clinically important differences when calculating estimates of sample sizes required for hand OA studies. Protocol developers should examine the published literature for estimates of variance that may be relevant for sample size estimation.

Conclusion

The purpose of these Task Force recommendations,is to provide evidence-based guidance on the design, execution and analysis of clinical trials in hand OA, where published evidence is available, supplemented by expert opinion where evidence is lacking. The Task Force also hopes that these guidelines will promote interest in, and encourage further investigation of, instruments and methodology for the assessment of clinical outcomes in hand OA therapeutic trials. The Task Force appreciates that there are insufficient data currently available to provide reliable guidance for all aspects of clinical trial design. In order that the body of knowledge will be expanded the Task Force supports the CONSORT statement encouraging full reporting of all randomized controlled clinical trials performed in patients with hand OA to ensure not only that the details of the design and conduct of the trials are available for external scrutiny, but also to allow free access to the full database.

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Glossary

ACR: American College of Rheumatology.
AIMS: Arthritis Impact Measurement Scales.
AUSCAN: Australian/Canadian Hand Osteoarthritis Index.
CMC: Carpo-metacarpal.
CONSORT: Consolidated Standards for Reporting Trials.
DIP: Distal Interphalangeal.
EuroQol: European Quality of Life Measure.
FIHOA: Functional Index for Hand Osteoarthritis.
HAQ: Health Assessment Questionnaire.
HUI: Health Utilities Index.
IGCP: International Good Clinical Practice.
IP: Interphalangeal.
LK: Likert.
MDGA: Physician Global Assessment.
MRI: Magnetic Resonance Imaging.
NHP: Nottingham Health Profile.
NRS: Numerical Rating Scale.
NSAIDs: Nonsteroidal Anti-Inflammatory Drugs.
OA: Osteoarthritis.
OARSI: Osteoarthritis Research Society International.
OMERACT: Outcome Measures in Rheumatology Clinical Trials.
PGA: Patient Global Assessment.
PIP: Proximal Interphalangeal.
PRO: Patient Reported Outcomes.
SACRAH: Scores for Assessment and quantification of Chronic Rheumatic Affections of the Hands.
SF-36: Short Form 36.
SIP: Sickness Impact Profile.
SRM: Standardized Response Mean.
SYSADOA: Symptomatic Slow-Acting Drug in Osteoarthritis.
VAS: Visual Analog Scale.