European Drug Guideline Series 5

Guidelines for the Clinical Investigation of Drugs used in Rheumatic Diseases

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CONSTITUTION OF THE WORKING GROUP

WHO REGIONAL OFFICE FOR EUROPE DRUG GUIDELINE SERIES
GUIDELINES FOR THE CLINICAL INVESTIGATION OF

DRUGS USED IN RHEUMATIC DISEASES

INTRODUCTION

Clinical evaluation of drugs which may be of value in the treatment of rheumatic diseases should follow generally accepted scientific principles as laid down in WHO Technical Report Series, No. 403 (1968)(a) and No. 563 (1975)(b). In the present draft, these principles are presented as guidelines for the clinical investigator.

These Guidelines have been drafted by a joint Working Group of the World Health Organization's Regional Office for Europe and the European League Against Rheumatism (EULAR), and have been revised in the light of comments received from the many rheumatologists to whom they were submitted, Member States in the European Region, Drug Regulatory Agencies and the Pharmaceutical Industry. It must be stressed that the consultations took place primarily within the European Region; it is entirely possible that the text will not reflect all the needs of investigators in other parts of the world.

The present text has drawn upon the literature and upon a document drafted for EULAR by Lequesne and Méry (1980), as well as upon guidelines published or drafted by regulatory agencies or regional bodies involved in drug regulatory matters (c), (d), (e), (f), (g), (h), (i); it must be emphasized, however, that this is not intended as a strict basis for regulatory guidelines. Some of the elements presented here, such as studies of mechanisms of action or risk/benefit relationships, may be of scientific or social importance but not relevant to particular regulatory systems. Like other Guidelines in the series, this text is intended for the use of clinical investigators and seeks to state what may currently be regarded as sound investigational standards for this particular group of drugs. It is realized that, in various of the fields with which it deals, alternative investigational approaches are possible and that others will be developed; the text thus has no mandatory character and in particular it is not intended to set any form of legal standard. It should therefore not discourage the development of new and better techniques. It does not seek to indicate which studies should be undertaken before a drug is admitted to the market, nor does it define in which order particular investigations should be performed, except where there are purely scientific or ethical reasons to follow a particular sequence. Regulatory standards are likely to be closely similar in some respects to scientific investigational standards, but they will necessarily depend in large measure on a country's drug legislation and will therefore differ in various parts of the world.
The text will be revised periodically as new scientific knowledge about this class of drugs accrues, or as principles and methods for the evaluation of drugs evolve.


A. GENERAL PRINCIPLES

Adequate drug therapy of rheumatic diseases presupposes an accurate diagnosis and an evaluation of the symptoms, nature and prognosis of the disease. There are a large number of drugs used in the treatment of rheumatic diseases and they differ in their therapeutic effect, adverse effects and mode of action. The pharmacotherapy of rheumatic diseases should ideally give relief from pain and stiffness, reduce the inflammatory activity and slow the progress of the disease. In some instances it may be difficult to differentiate between the analgesic and anti-inflammatory effects; it may also be difficult to distinguish anti-inflammatory effects from other mechanisms of action, e.g. in the case of immunosuppressive/cytostatic drugs.

Definition of rheumatic diseases

The term rheumatic diseases refers to more or less well defined groups of diseases involving articular, periarticular, muscular and connective tissues, and including a variety of painful disorders of the locomotor system, most of them potentially chronic.

Groups of rheumatic diseases used for clinical testing

For the present purpose the following groups of diseases generally used as models for clinical testing can be distinguished:

- inflammatory diseases of the joints of the extremities and spine, including rheumatoid arthritis, ankylosing spondylitis and related conditions; other systemic connective tissue disorders;
- certain metabolic joint diseases, e.g. gouty arthritis and chondrocalcinosis;
- the degenerative arthropathies, involving the joints of the extremities and spine;
- soft-tissue or non-articular rheumatism, including diseases of muscles, tendons, tendon sheaths; painful conditions of muscles caused by postural, occupational and other factors.

Principles to be considered

Ethics

All drug trials should be conducted in accordance with the Helsinki declaration (j).

Before undertaking a trial of a new drug for the treatment of rheumatic diseases, it is important to consider whether the drug in question is likely to offer any advantage over drugs already available (see Appendix 3, point 22); this applies particularly to non-steroidal anti-inflammatory drugs of which there are already a great number. The possible place of the trial or

experimental drug in the spectrum of drugs used in the treatment of rheumatic diseases also has to be considered so that studies may be planned in a manner most likely to benefit the rheumatic population and least likely to create risks.

Objectives

Studies of (antirheumatic) non-steroidal anti-inflammatory drugs (NSAID) and disease-modifying antirheumatic drugs (DMARD) should be planned to establish, in the short and long term:

1. Efficacy (relief of pain and stiffness and improvement in function; prevention of joint deterioration).
2. Safety
3. Balance between (1) and (2)
4. Relative efficacy and safety, the trial drug being compared with at least one reference drug.
5. Mode of action

Type and design of trials

The characteristics of the disease to be treated should be considered in the design of clinical trials (see later sections of these guidelines). Studies can conveniently be classified into phases; the phases recognized for the purposes of this series of WHO Guidelines comprise:

(a) Initial studies in man (human pharmacology)
(b) Pilot therapeutic trials and dose-finding studies
(c) Main therapeutic trials
(d) Long-term studies and special studies

These phases are further defined in Appendix 1.

Background information on the trial drug and its anticipated relevance in treatment, as well as the objectives and anticipated problems of the trial, should be set out when a study is designed.

The patient sample should be as homogenous as possible. If subgroups can be identified they should be stratified. There should be a need for drug treatment. The possible effects of non-drug therapy (physiotherapy, surgery, mobilization etc) or changes in life-style with possible therapeutic influence should be taken into account in the design of studies.

Selection of patients

Satisfactory criteria for the diagnosis of the condition under study should be set out and fulfilled by patients entered into the trial.
The description of patients taking part in the trial should include age, sex, weight, height, and the main characteristics of the disease (see below). Disease complications and concurrent treatment should be recorded so that their effects, if any, on the result of treatment with the new drug may be analyzed later.

In view of the age structure of the rheumatic population, it is particularly important that elderly patients be studied from an early phase, both in kinetic and therapeutic investigations.

**Evaluation, measures of efficacy**

Before any clinical study is undertaken, the investigator should decide what type and degree of response will be regarded as clinically useful.

In investigations of drugs used in rheumatic diseases it is particularly important not to place excessive weight on "objective" responses as against well-validated "subjective" responses; the latter may be a more sensitive indication of the patient's well-being.

Measurements should be standardized as far as possible, and ideally be undertaken by the same investigator and at the same time of day on each occasion. All tests should be defined exactly, i.e. how measurements should be made and how questions should be asked. This is especially important in a multi-centre trial where differences in approach between the various centres can all too easily occur. Questions put to patients should be standardized, with an alternative way of asking each question if at first it is not fully understood.

**Withdrawals from the trial because of adverse reactions, lack of effect, lack of patient cooperation**

The reason for all deliberate withdrawals and dropouts should be clearly recorded; they should be scored as failure of, or intolerance to, the trial drug in the statistical analysis, unless they are clearly unrelated to therapy (e.g. intercurrent illness or injury, secondary exclusion, migration).

**Adverse reactions and side effects**

Adverse reactions and side effects observed by the investigator and elicited from the patients in response to the question, "How is/are the medicine/tablets suiting you?", should be recorded. In addition, all medical events occurring during the course of the trial, even if not apparently related to the trial drug, should be recorded.

**Trial Coordinator**

A trial coordinator, or a third party, not involved in assessment of the results of the drug trial or otherwise participating in the trial, is valuable for obtaining informed consent from the patient, carrying out random allocation of patients to treatment or control groups and, in the event of serious or unexpected adverse effects, breaking the code in order to identify whether the patient is on the test drug or on placebo/reference drug.
Interpretation of results

The clinical investigator should be alert to the possible distinction between statistical significance and clinical importance. The term "significant" is best reserved for describing statistical significance.
B. INDIVIDUAL RHEUMATIC DISEASES

B.1. RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis is a variable disease both as regards its outcome and its day-to-day severity. This complicates the interpretation of results of drug trials.

Selection of patients (Ropes et al., 1959)

Patients with "definite" or "classical" rheumatoid arthritis (e.g. as defined using ARA criteria) may be included in the clinical trial. It may be necessary to also include as a special group those with "possible" rheumatoid arthritis in order to study the effects of drugs on early disease. The main characteristics of the condition, such as the presence of rheumatoid factor, duration of disease, stage of progression, the presence or absence of extra-articular manifestations (such as subcutaneous nodules) and the levels of the laboratory indices of disease activity should be indicated. If certain joints have been treated surgically this should be specified. Past and current drug therapy of any type should be noted. Stratification may be necessary, but in view of the large number of variables this may be difficult unless a large number of patients are included.

Criteria for remission

Criteria for remission should be set in advance, e.g. along the lines set by the ARA (Pinals et al., 1981, Fries, 1983).

I. Studies of non-steroidal anti-inflammatory drugs (NSAID) in RA

As the main effect of the NSAID is analgesic and anti-inflammatory, the response is symptomatic and therefore may be difficult to assess because most of the measurements are subjective. It is also difficult to discriminate between the analgesic and anti-inflammatory effect.

The NSAID are quick acting and maximum efficacy is usually rapidly obtained. Some of these drugs, however, have a long half-life and it can take weeks before "steady state" is reached, particularly in the joint tissues.

Particularly in crossover studies, patients stabilized on disease-modifying drugs or corticosteroids can be included, if these drugs are maintained at the same dose throughout the trial of the NSAID. Patients should not be given additional NSAID other than the drug(s) under investigation.

A simple analgesic without anti-inflammatory activity, such as paracetamol, may be given as a "rescue drug" when needed.

Type and design of trials

See Appendix 1.
Duration of trials

An impression of the efficacy of these drugs can usually be gained in a study, lasting 1-3 weeks. This impression is however only likely to be reliable where one is dealing with NSAID closely related to existing agents. A drug which is novel will need to be studied for a much longer period in order to determine to what extent, if any, it differs from existing agents as regards efficacy, the time taken to reach an optimal effect, or safety. Hypotheses as to possible superiority or greater safety will similarly demand a much longer period of investigation.

Evaluation, measures of efficacy

In a short term study of NSAID it is recommended to use a reasonable number of validated tests, performed both in the washout period (pre-trial state) and during treatment. None of the measures in current use are ideal, but some of those which have been validated and proven helpful are listed below:

1. Measurement of pain on movement or during weight-bearing using a visual analogue or four point scale.
2. Rest pain or night pain (number of times woken by pain during the night)
3. Duration of morning stiffness
4. Grip strength
5. Measurement of proximal interphalangeal (PIP) joint circumference
6. An articular index, e.g. that developed by Ritchie et al., (1968)
7. A functional index (objective or subjective) e.g. that developed by Lee et al., (1973)
8. Overall evaluation by the patient in comparison with his or her pre-trial state (e.g. "better", "worse", "unchanged").
9. Overall evaluation by the physician.

Measurements should ideally be taken at the same time of the day on each occasion.

II. Studies of disease-modifying antirheumatic drugs (DMARD) in RA

These drugs are used in an attempt to control disease activity and halt radiological progression. They have also been called remission-inducing or slow acting drugs. The indications for their use and the stage of rheumatoid arthritis at which they are an appropriate treatment are still not satisfactorily established. For the purposes of clinical trials, the patient should have "classical" or "definite" rheumatoid arthritis as defined by the American Rheumatism Association (ARA), and meet one of criteria 1-3 below:

2. Failure to respond to NSAID.

3. Evidence of disease progression, e.g. development of erosions and/or a progressive decline in functional capacity.

As the criteria are difficult to define exactly, any individual variation should be clearly stated.

NSAID which are claimed to have disease modifying properties should be studied both as NSAID and DMARD.

The objectives of trials with disease-modifying drugs may include the study of:

(a) the effect on clinical disease activity (as listed in the section on NSAID);

(b) effects on joint disease, and on bone and cartilage destruction. Radiological progression is difficult to assess (Gofton, 1983); the radiological method is more reliable when counting new lesions (i.e. erosions) than when counting the steps from one radiological stage to the next (Grindulis et al., 1983). Alternatively, overall methods for assessing the state of the joint can be used, e.g. as proposed by Larsen et al. (1977). Improved methods for assessing the state of the joint, based on new technologies, are being developed;

(c) effects on extra-articular manifestations of the disease;

(d) adverse reactions;

(e) influence on efficacy or safety of concurrent treatment (e.g. with corticosteroids or a second disease-modifying drug);

(f) benefit/risk relationships, evaluated both early and late;

(g) possible mechanisms of action as indicated by laboratory measures.

Type and design of trials

See Appendix 1. All three basic types of trial are likely to be needed, that is:

(a) Open
(b) Single-blind
(c) Double-blind

In general, a potential disease-modifying drug should be compared with another drug of the same type and not with an NSAID alone. Retrospective controls are unsatisfactory.

Patients used for comparison may be on (i) placebo (ii) NSAID or (iii) another disease modifying drug. Placebo control should probably be used only in the phase of early clinical trials and patients on placebo who are clearly deteriorating should be withdrawn from trial.
Blinding can be difficult to maintain over a long period especially if one of the drugs has to be given by injection (e.g. sodium aurothiomalate) or if the drug has a characteristic feature (e.g. smell) which identifies its presence in the urine. Methods are available to avoid these difficulties (see Appendix 1, para. 3).

Both single centre and multi-centre studies are likely to be needed.

A cross over design is not appropriate for disease-modifying drugs which are slow-acting with a long wash-out period.

Duration of trials

Duration of a trial should depend upon the nature of the trial drug and the question to be answered by the trial. In principle, trials of DMARD should be planned to last for at least 6 months to determine efficacy and preferably 12 months to obtain information on longer-term effects. Non-responders should usually be withdrawn within 4-6 months. The criteria for lack of responsiveness should be set in advance for each trial. If placebo is used, ethical considerations will restrict the duration of the trial. It should be decided in advance whether drop outs should be replaced.

Long-term and "post-marketing" studies of both wanted and unwanted effects are of especial importance where a drug is expected to be disease modifying.

The frequency and type of adverse reactions may differ with the length of exposure to the drug and/or be dependent upon the total dose given. Uncommon idiosyncratic adverse effects remaining unidentified during earlier clinical trials will often be recognized and confirmed only by long-term work after a drug has come into general use.

Follow-up is for similar reasons desirable. Patients who have had the trial drug withdrawn because of adverse reactions or who have dropped out of the trial will usually need to be followed up to determine their subsequent course at least until the trial ends. Patients whose disease has remitted during the course of the trial will need to be followed up to observe the course of the disease in the post-trial period and if treatment is not continued to assess how long the remission is maintained before there is re-activation of rheumatoid arthritis.

Evaluation/measures of efficacy

Measures are similar to those used in trials of NSAID, supplemented by others relating to the objectives as defined earlier in this chapter. Objective measurements are of especial value in these trials. Correlations, if any, between clinical efficacy and available laboratory measures, changes in which may reflect modification of the disease process, should be looked for.

In the case of a drug supposed to have disease modifying properties in RA, it will only be reasonable to continue to study it if early work shows a response with respect to at least two of the following three measures:
(a) decrease in sedimentation rate;

(b) decrease in alpha-2 globulins, gamma-globulins, haptoglobin or reactive protein;

(c) clinical improvement in a small series of patients, persisting for some weeks after withdrawal of treatment.

III. Studies of cytostatic drugs in RA

Most of the principles set out above for DMARD studies in general apply when investigating cytostatic drugs. Because of the risks inherent in the use of this type of drug (notably bone-marrow depression, sterility, mutagenesis and perhaps oncogenesis), trials are usually limited to patients with disease unresponsive to standard therapy or who have serious complications (e.g. vasculitis or amyloidosis). Multicentre trials may be most appropriate because of the small number of eligible patients available in any given centre. Several areas need further investigation; they include the proper indications for cytostatic therapy, mechanisms of action, the type of drug to be selected for each individual type of case and the development of optimal dosage schedules, e.g. with intermittent therapy.

Before commencing any trial with cytostatic drugs, the importance of the proposed study should be weighed against the possible risks, e.g. the risk of long-term induction of malignancies, sometimes many years later. A careful follow-up of patients given cytostatic therapy is required in order to detect possible adverse effects; some of these malignancies may occur many years after withdrawal of the drug, particularly after long-term therapy.
B.2 ANKYLOSING SPONDYLITIS (AS)

Trials of NSAID may be undertaken on patients with AS who fulfil accepted diagnostic criteria. Most of the studies will comprise "main therapeutic trials" and "long term studies", since earlier work will usually have been performed in RA.

It is difficult to define the activity of this disease satisfactorily. None of the available criteria are optimal and it has not yet been decided which should be recommended, e.g. the New York criteria (Bennett and Wood, 1968) or the simplified "fundamental criteria" (Lequesne and Méry, 1980). Modified criteria are included also in FDA guidelines. Active disease should be painful including axial pain preferably with restricted chest and spinal movements; this will include 66% of all patients with ankylosing spondylitis (Moll and Wright, 1976). Disease activity can be measured in terms of joint and back pains, morning stiffness and secondary restricted movements. Before entering into a trial it is recommended that the NSAID which patients are currently using be withdrawn to demonstrate the presence of active disease. Patients with ankylosing spondylitis may be eligible for trials with disease-modifying drugs, but it is extremely difficult to measure long-term effects of drugs in this disease.

Evaluation, measures of efficacy

None of the measures in current use are ideal, but some of those which have been validated and prove helpful are listed below.

(a) Objective evaluation

1. Recording of spinal movements in all three planes (anterior flexion and posterior hyperextension, lateral flexion, rotation)
2. Chest expansion

(b) Subjective evaluation

1. Visual analogue scale evaluating spinal pain and pain in the peripheral joints (if present) during use and weight-bearing.
2. Night pain - to be assessed either using a four-point scale or by stating the number of times the patient is woken by pain.
3. Duration of morning stiffness.
4. Patient's overall opinion.
5. Physician's overall opinion.

Other methods, which may be more specific, are likely to result from new technology.
B.3 PSORIATIC ARTHRITIS (PA)

Main therapeutic trials both of NSAID and slow-acting disease modifying preparations can be undertaken in psoriatic arthritis; the general rules and basic principles are the same as for trials in patients with rheumatoid arthritis and/or ankylosing spondylitis.

Since this is one of the less common rheumatic diseases, experience in the design and performance of methodical studies is limited; the variability of the disorder also complicates the conduct of investigations and makes stratification advisable where possible. Multi-centre studies are particularly appropriate for the study of this condition, since most centres have only a small number of patients.

Patients to be included should be those with both psoriasis and peripheral polyarticular arthritis, either assymetrical or (less typically) symmetrical. Patients with arthritis mutilans and oligoarthritis are not suitable for inclusion.

With some exceptions, the measures recommended to test the therapeutic response are similar to those used in rheumatoid arthritis. However, morning stiffness is not a uniform feature of psoriatic arthritis, measurement of PIP joint circumference is often not feasible (sausage fingers, mutilating changes) and asymmetry in joint involvement may make it difficult to assess the number of pairs of swollen finger joints.

The influence of trial drugs on the skin and nail manifestations of psoriasis should ideally be assessed by a dermatologist or using criteria determined in advance by a dermatologist. Any changes in skin lesions should be compared with the effect of the drug on the joint manifestations in order to arrive at an overall evaluation.
The term "juvenile chronic arthritis", which in fact covers a heterogenous group of disorders, was introduced during the Workshop on the Care of Rheumatic Children held under the auspices of WHO/EULAR in 1977. (EULAR monograph Series No. 3, 1978).

It has become customary to characterize the disease by its mode of onset, which may follow any one of three patterns:

1. systemic, with fever and at least one other feature such as typical rash, hepatosplenomegaly and lymphadenopathy;

2. polyarticular (involving five or more joints in the first three months);

3. pauciarticular (involving less than five joints in the first three months).

However, the pattern of illness can change, e.g. the systemically ill child may go on to develop polyarthritis, while the pauciarticular form may become polyarticular.

Further sub-groups including spondylitis, psoriatic arthritis and enteropathic arthritis as well as sero-positive juvenile arthritis also exist and require special studies.

The exact type of case being studied needs to be defined carefully prior to an investigation, and patients should be characterized among other things with respect to the mode of onset; they should be stratified with respect to their current state prior to their allocation to therapy groups. For all these purposes a comprehensive entry form should be employed and completed for each patient.

For studies of long duration (e.g. six months or more) it is important to re-check the pattern of illness in the same way at the end of the observation period.

A drug study in children will generally not be appropriate before the pilot therapeutic trials and as a rule the main therapeutic trials have been completed in adults. Assessment in children is not easy as pain is often minimal and morning stiffness is not recognized by young children, so that one has to rely on parental comments on morning slowness. The Ritchie index is not entirely satisfactory particularly in children with few joints involved, so that an index of active joints involved is probably better (Kvien et al., 1982, Moran et al., 1979). Functional grading shows only major differences and is of no use in short-term studies. Function tests are useful provided there is appropriate involvement. Parental and physician's assessments are extremely valuable. There is also a major ethical problem in giving a new drug to a child who cannot give his or her informed consent. The problem of remission is also difficult; as yet there are no criteria generally agreed upon for this.
It is important that pharmacokinetic studies in children are undertaken when the main therapeutic trials have been completed in adults. Drug metabolism tends to change around puberty; the age at which children are included in studies is therefore important; no definite lower age limit has been defined. These pharmacokinetic studies should, whenever possible, be combined with an efficacy study and a careful watch for side effects which may arise. This would correspond to a "Segment 1" Study of the American Collaborative Group for Drug Trials in Rheumatic Children (Brewer and Giannini, 1982).

I. Studies of non-steroidal anti-inflammatory drugs (NSAID) in JCA

Type and design of trials

See Appendix 1.

As soon as appropriate pharmacokinetic and initial clinical studies in children have been completed, double blind comparative studies should be undertaken.

A new NSAID should be compared against aspirin and/or against one of the earlier NSAID generally accepted for use in children such as ibuprofen or naproxen.

Evaluation, measures of efficacy

Examples of assessments which have proved valuable in controlled trials in JCA are:

1. An articular index (e.g. that of Kvien et al., 1982)
2. Parental opinion of child's state
3. Physician's opinion of child's state

Other measures which may be useful are:

1. Duration of morning slowness as graded by a parent or, in the case of an older child, by itself
2. Degree of pain as graded by parent or child (visual analogue or point scale)
3. Functional tests: Grip strength, using an appropriately sized machine, can be used if the upper limbs are affected, walking time if the lower limbs are affected.
4. Goniometry at various sites (knee, ankle, wrist as appropriate)
5. In cases with pyrexia, measurements of body temperature.
6. Laboratory measurements.
II. Trials of disease-modifying anti-rheumatic drugs (DMARD) in JCA

The indications for the use of these drugs will include poly or pauciarticular juvenile chronic arthritis and in selected cases also systemic forms; patients selected for study should have:

1. Continuing activity of the disease, since in a proportion of children spontaneous improvement can occur, a pre-treatment observation period of 3–6 months is advisable.

2. Evidence of disease progression, e.g. involvement of additional joints, growth disturbance, deterioration of the X-ray picture or progressive decline in functional capacity.

Radiological criteria for sero-negative juvenile chronic arthritis have not been established and for the present it would seem reasonable to try and use Steinbockers classification with a sub-group for:

(a) alterations in growth
(b) periosteal reaction

Type and design of trial

See Appendix 1.

Because most centres have only a few patients available, it can be useful to arrange in the first instance a multi-centre trial using a common basic trial structure but with each centre focusing on a different problem.

Evaluation, measures of efficacy

Clinical and laboratory assessment would be as for NSAID but X-ray measurement should be of an affected site and the corresponding contralateral site, preferably taken on the same film, and repeated approximately annually.
B.5 SYSTEMIC CONNECTIVE TISSUE DISEASES

These include systemic lupus erythematoses, Sjögren syndrome, mixed connective tissue disease, the vasculitides, progressive systemic sclerosis and dermatomyositis/polymyositis. They will not be dealt with in detail in these Guidelines.

Controlled clinical trials with NSAID, disease-modifying antirheumatic drugs, glucocorticosteroids and cytostatic drugs in the systemic connective tissue disorders should be performed according to principles analogous to those used for rheumatoid arthritis. Some of the systemic connective tissue diseases are rare and therefore multicentre trials are (often) recommended to obtain a sufficient number of patients and to get comparable controls. Several different diagnostic criteria are in use for these conditions and therefore common criteria must be agreed for diagnosis, classification and stratification.

Trials will often be long-term, comparing the effect of different drug combinations on the course and long-term outcome of the disease. Survival time may be one of the measures used in these trials. The effect on serious extra-articular complications may be another. Frequencies of side effects should also be compared. The connective tissue disorders are usually not suited for short-term studies of efficacy of NSAID but long-term tolerability of these drugs can be studied. Most trials are aimed at studying different disease-modifying drugs or combinations of such drugs including their combination with corticosteroids. Trials should be long-term, double-blind, parallel, comparing effect and safety in otherwise comparable sub-groups. Long-term studies to detect possible development of tumours or malignancies are recommended for cytostatic drugs; such complications may occur many years after treatment.
B.6 CRYSTAL-INDUCED SYNOVITIS (CIS)

This term covers both gout and pseudo-gout (chondrocalcinosis articularis, pyrophosphate synovitis). Pseudopout, because of its variability, is not suitable for methodical study and will not be discussed here.

In gout, drugs may be used to relieve the acute attack or to treat the chronic condition (relieving chronic symptoms and/or preventing acute attacks). The exact goal of the investigation should be well-defined, i.e. the study of the acute attack should be clearly distinguished from that of the chronic condition, though it is often possible to study both in the same patient.

Anti-inflammatory drugs are more likely to be useful for the former purpose, drugs affecting uric acid metabolism for the latter, but this is only a generalization; some drugs have both types of effect.

I. Studies of non-steroid anti-inflammatory drugs (NSAID) in CIS

Type and design of trials

Early pilot trials can be open, but later studies should be double-blind.

It is difficult to study the ability of drugs to prevent or shorten or relieve the acute attacks since such attacks occur unpredictably and are self-limiting.

In acute attacks parallel control studies are needed. Studies are likely to take place in primary health care setting or on a multicentre basis. The test drug should be compared with colchicin or with another standard NSAID in which efficacy in acute attacks has already been established. Trials will be brief, their duration being related to that of the attack.

In patients with chronic symptoms (chronic arthritis in gout), cross-over studies can also be used where feasible. Such studies should last for a number of weeks.

Selection of patients

Patients who are included in trials with NSAID should have symptoms relating to the joints and fulfill the criteria for the diagnosis of primary gout or pseudogout. The criteria used should be stated.

Patients included in short-term studies should have a history of acute attacks.

Patients included in long-term, parallel or cross-over studies, should have chronic pain, stiffness or swelling in joints of at least 2-3 months duration.

Evaluation, measures of efficacy

Objective and subjective measurements are similar to those used in rheumatoid arthritis. They may include:
(a) **Objective measurements:** Swelling and tenderness in the joints, range of motion and grip strength can be recorded in the same manner as in rheumatoid arthritis.

(b) **Subjective measurements:** A visual analogue scale can be used for grading pain and stiffness in the peripheral joints. Patient’s and physician’s overall preference in each treatment period should be recorded.

Daily assessments may be necessary during acute attacks.

II. **Studies of drugs normalizing metabolism or serum/tissue levels and body pool of uric acid in CIS**

Two types of drugs are used:

1. Drugs increasing the renal excretion of uric acid (uricosuric drugs).
2. Drugs inhibiting the synthesis of uric acid by enzyme inhibition (inhibition of xanthine oxidase).

**Type and design of trials**

Controlled trials with these drugs should usually be double blind, long-term, parallel studies. They can be conducted with or without the simultaneous use of colchicin or other NSAID. Salicylic acid, ascorbic acid and other compounds with a known influence on uric acid levels should be avoided. Diets and beverages should be standardized and as far as possible kept unchanged throughout the study. The body weight should be kept approximately constant. Multi-centre trials may be necessary.

In parallel studies, the control group should be comparable to the treatment group with respect to pre-study severity and frequency of acute attacks.

Drugs available to date for normalizing uric acid metabolism are very prone to induce an increase in the number of gouty attacks during the first few months of use. Trials with these drugs should therefore last long enough to allow clinical measures to be recorded after this critical phase.

**Selection of patients**

Only patients with primary gout should be included. Patients with hyperuricemia due to another primary disease or other drug treatment (secondary gout) should be excluded. The patients should fulfill the diagnostic criteria for gout. Patients with gout should have consistently elevated serum uric acid levels and preferably have chronic arthritis with tophi so that it is possible to assess long-term clinical benefit.

**Evaluation and measures of response**

Possible clinical measurements may include:

1. Frequency of acute attacks
2. Disappearance of visible tophi
3. Reduction in chronic joint symptoms.
Relevant laboratory measures are:

1. Serum levels of uric acid.
2. Excretion of uric acid in the urine (preferably for the enzyme inhibitors).

Radiological assessment of gouty joint damage should be undertaken.

**Measures of drug safety**

Monitoring should include renal and hepatic function tests, and any safety measures the need for which may be suggested by the nature of the drug.

**Interactions**

Other drugs which could interact with the uricosuric drugs in the kidney should be avoided, (e.g. penicillin and other antibiotics and drugs with renal tubular excretion). The possibility of interactions with other drugs, e.g. allopurinol and purine antagonists, should be kept in mind.
B.7 OSTEO-ARTHRITIS (OA)

Painful osteoarthritis of the large joints provides a good model in which to test the analgesic effect of a new NSAID, though the mode of action of these drugs on pain remains largely unknown. The small joints affected by OA are less responsive and may indeed show no response at all to analgesics or NSAID.

DMARD are currently being studied in OA both for the effects on pain and longer term influence, if any, on radiographic deterioration.

I. Studies of non-steroidal anti-inflammatory drugs (NSAID) in OA

Patients with OA of the hip and the knee may usefully be included in clinical trials of the efficacy of NSAID. OA is a painful degenerative joint disease, but moderate joint inflammation may occur during the course of the disease. The basis for the use of these drugs is therefore their analgesic as well as their anti-inflammatory activity.

Type and design of trials

These are as for rheumatoid arthritis.

Selection of patients

Patients with painful osteo-arthritis of the hip and/or the knee are most suitable for inclusion in such studies. Other forms of osteo-arthritis are less consistently painful and perhaps not so suitable for trials of analgesic drugs and NSAID. However, cases of painful osteo-arthritis at other sites could be included in long-term large scale trials in which the main aim is to evaluate drug safety.

Criteria for definitive diagnosis of osteo-arthritis of the hip and knee should be set and the criteria used (see for example Lequesne, 1982) should be fulfilled.

The disease status should include pain each day for more than three months duration but patients should not be so severely affected that surgery is likely to be needed in the near future. The radiological stage and the duration of pain should be stated as well as the other sites affected by osteo-arthritis. Concomitant disease and therapy should be recorded. Patients stabilized on physical therapy for more than one month can be included.

Exclusions will be necessary with respect to:

- hospital patients on bed-rest; however, such patients can be included in the first phases of the study or (for injectable forms) after the improvement in response to bed rest has become stabilized;
- those with a past history of trauma at the site of osteo-arthritis who are seeking compensation for their injury;
- those who have had intra-articular corticosteroid injections to the target joint during the previous two months.
Duration of the trials

From one to three weeks are usually sufficient to assess the efficacy in a controlled trial; to evaluate the adverse reactions, open long term studies on a larger population are necessary.

Evaluation, measures of efficacy

The following measures are examples of those which have been found useful and statistically valid for drug trials in osteo-arthritis (Lequesne, 1982):

- index of severity of hip and knee disease (e.g. as proposed in Table 1);
- investigator's overall opinion;
- pain on visual analogue scale;
- patients overall opinion;
- walking time.

In cases affecting the knee, the time taken to climb stairs is a better measure than the walking time.

II. Studies of disease-modifying anti-rheumatic drugs (DMARD) in OA

To assess the possible influence of a new drug on the slowly progressive course of osteo-arthritis, long-term controlled trials, perhaps lasting at least 3 and if possible 5 years, will be necessary. It will be important to have positive evidence from long-term animal studies or other indications of efficacy and safety before embarking on such difficult long term controlled trials in osteo-arthritis.

Type and design of trials

Neither open nor cross-over trials will be useful. Randomized double-blind control trials with parallel groups should be used. As, so far, there are no known drugs which can definitely modify the course of osteo-arthritis, the use of a placebo control is justified. Patients already taking NSAID or analgesics or receiving physiotherapy can continue to do so, if it is needed, but details of treatment should be recorded.

Selection of patients

As the narrowing of the joint space on X-ray will be one of the main assessment criterion, only osteo-arthritic joints with a measurable joint space should be included. Only osteo-arthritis of a primary type without significant dysplasia should be included in the trials.

One should exclude patients under the age of 50 years (progression of OA usually being slow in younger patients) and patients in whom surgical treatment for an osteoarthritic joint is likely in the near future.

Duration of trials

See general introductory remarks above.
### TABLE 1

**INDEX OF SEVERITY FOR OSTEO-ARTHRITIS OF THE HIP AND OF THE KNEE**

*(Lequesne. 1982)*

<table>
<thead>
<tr>
<th>Points</th>
<th>1. Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(a) Nocturnal pain</td>
</tr>
<tr>
<td></td>
<td>- only on movement or in certain positions 1</td>
</tr>
<tr>
<td></td>
<td>- without movement 2</td>
</tr>
<tr>
<td>1</td>
<td>(b) Duration of morning stiffness or pain after getting up</td>
</tr>
<tr>
<td></td>
<td>- less than 15 minutes 1</td>
</tr>
<tr>
<td></td>
<td>- 15 minutes or more 2</td>
</tr>
<tr>
<td>1</td>
<td>(c) Remaining standing for 30 minutes increases pain</td>
</tr>
<tr>
<td>1</td>
<td>(d) Pain on walking:</td>
</tr>
<tr>
<td>1</td>
<td>- only after walking some distance</td>
</tr>
<tr>
<td>2</td>
<td>- very early after starting to walk and increasing</td>
</tr>
<tr>
<td>1</td>
<td>(e) Pain or discomfort when getting up from the sitting position</td>
</tr>
<tr>
<td></td>
<td>(in cases affecting the hip: after prolonged sitting)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>2. Maximum walking distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>- More than 1 km, but limited</td>
</tr>
<tr>
<td>2</td>
<td>- About 1 km (about 15 minutes)</td>
</tr>
<tr>
<td>3</td>
<td>- From 500 to 900m (about 8-15 minutes)</td>
</tr>
<tr>
<td>4</td>
<td>- From 300 to 500m</td>
</tr>
<tr>
<td>5</td>
<td>- From 100 to 300m</td>
</tr>
<tr>
<td>6</td>
<td>- Less than 100m</td>
</tr>
<tr>
<td>+1</td>
<td>- With one walking stick or crutch</td>
</tr>
<tr>
<td>+2</td>
<td>- With two walking sticks or crutches</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>3. Activities of daily living*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2</td>
<td>(a) Hip</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you put on socks by bending forward?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you pick up an object from the floor?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you go up a standard flight of stairs?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you get into and out of a car?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>(b) Knee</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you go up a standard flight of stairs?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you go down a standard flight of stairs?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you squat completely?</td>
</tr>
<tr>
<td>0 to 2</td>
<td>- Can you walk on uneven ground?</td>
</tr>
</tbody>
</table>

*Point score: No difficulty 0 |
With difficulty 1 (or 0.5, or 1.5) |
Impossible 2
Evaluation, measures of efficacy

The main measurement of efficacy will be the changes in the width of the joint space and the degree of sub-chondral bone deterioration seen on the weight-bearing X-ray over a period of years. Other parameters are similar to those used for NSAID in OA, including the limitation of movement in affected joints. Additional measurements which may be used include:

- daily dose of any NSAID or analgesics which may be required;
- the proportion of patients requiring surgical treatment during the course of the trial.
B.8. SOFT TISSUE AND SIMPLE EXTRA-ARTICULAR RHEUMATIC CONDITIONS

This term includes various conditions such as epicondylitis, sprains, injuries, myalgia, shoulder pain, low back pain (without evidence of structural disorder) and algodystrophy. These conditions are difficult to define and are often influenced by psychological factors. These features make controlled trials problematical and demand a careful classification and stratification.

It is not known to what extent an inflammatory component is present in many of these conditions and in the majority of these cases, an analgesic effect is more important than an anti-inflammatory effect.

Drugs employed in these disorders are mostly analgesics and NSAID; sometimes psychotropic drugs are used. There are however little relevant data and few reports of clinical trials in these conditions. The lack of a methodological data base makes it difficult to set out reasoned proposals for clinical trials. Nevertheless certain points should be taken into account and these are summarized below.

Definition of objectives, population and methods

Because of the above-mentioned problems, the goal of any clinical trial in soft tissue diseases has to be very clearly chosen and defined; there is an important difference between short-term immediate pain relief, which may be all that is wanted in some of these conditions, and maintenance of longer-term pain control, e.g. such as may be required in chronic low back pain.

The criteria for including patients in a study or in particular diagnostic sub-groups should be clearly defined; patients with different diagnoses or aetiologies should not be included in the same sub-group, e.g. shoulder pain can be of different types and have different causes.

Trials should be randomized.

Factors relevant to the prognosis should be recorded and used to form sub-groups, e.g. age, and whether the patients are in hospital or not, can be of great importance. Concomitant treatment, whether medicinal or not, should be left unchanged.

Evaluation, measures of efficacy

Spontaneous pain, registered on a visual analogue scale, is the primary measure. In certain cases it may be possible to quantify one or more of the following:

- patient preference for one treatment
- pain provoked by pressure or motion
- limitation of movement
- functional capacity
- limitation of activities of daily living (subjective)
- changes in mental state.
C. INTRA-ARTICULAR THERAPY

Substances used for intra-articular treatment in the rheumatic disorders currently include:
- corticosteroids
- osmic acid
- radio-isotopes
- hyaluronic acid
- certain enzymes

Type and design of trials

The principles and rules concerning the necessity for controlled trials, double blind evaluation and appropriate methods of measurement are the same as those applicable to systemic therapy.

Comparative studies should be carried out, either

(1) in the form of intra-patient left/right studies; these are feasible only if the joint involvement is bilateral and approximately symmetrical. The active drug is administered on the one side, the reference drug or placebo on the other. The possibility of a systemic effect due to resorption should be considered.

or

(2) using two parallel groups of patients.

Evaluation, measures of efficacy

Special attention must be paid to (a) the duration of the improvement attained and (b) the possibility of deterioration (clinical and/or radiological) of the joint after repeated local treatment which may not become apparent for several years.
GENERAL NOTE ON APPENDICES

Since many of the studies organized with drugs in this field involve practitioners and specialists who have no prior experience in this type of research, the Appendices which follow provide some background or general information which may be useful for the relative novice in this investigational field. Some of the general material provided is naturally relevant to all forms of clinical drug trials and not specific to the area of "antirheumatic" drug investigation.
APPENDIX 1

PHASES AND DESIGN OF CLINICAL STUDIES

1. PHASES OF CLINICAL INVESTIGATION

The following division of clinical investigation into phases has been drawn up with the field of rheumatic diseases in mind. However, it corresponds approximately to the classification widely used in the literature. For a more extensive discussion see WHO Technical Report Series Nrs. 403 and 563.

**Initial studies in man**

These generally comprise initial investigations on a few healthy volunteers and/or on a small number of hospitalized patients in order:

- to confirm the findings in animal experiments
- to determine the approximate dose
- to obtain initial data on pharmacokinetics.

**Pilot therapeutic trials and dose-finding studies**

These investigations involve a larger number of patients; they are often carried out as open studies on patients in hospital. They are designed to obtain reliable basic data on matters which include the following:

- pharmacokinetics/dynamics
- presence of a therapeutic effect; this may involve the first comparison with a placebo
- dose-response curve and dose-ranging studies; with or without placebo; elderly patients should be included if the drug is likely to be used in this age group
- an impression of the potential indications for the use of the drug
- principal short-term adverse reactions to drug
- major reasons for non-response
- possible interactions with other drugs.

**Main therapeutic trials**

Before starting these trials there should be critical appraisal of work in the earlier phases to ensure that there is a therapeutic effect and that this (and the effects observed on laboratory parameters) justify further studies.
The main trials involve:

- Controlled studies with a sufficient number of patients to reach statistical significance and avoid type II error (i.e. the risk that a difference which is indeed present between two groups will fail to be demonstrated). The dose range of the trial drug believed to be optimal should be employed.
- Comparison with active reference drugs (and perhaps further placebo trials) within appropriate dose ranges in relation to the dose response curve of the trial and reference drug.
- Study of individual preferences (in cross-over studies only).
- Controlled withdrawal studies (where appropriate)

Long term studies and special studies

Further studies (including post-marketing evaluation and surveillance) involve:

- Continued controlled trials to broader knowledge of the therapeutic effect, indications and adverse reactions.
- Trials for new indications.
- Studies in special subgroups of patients, e.g. elderly patients, diabetics, children and other groups at special risk
- Long term efficacy/safety studies which in chronic diseases are of particular importance in view of possible fluctuation in the disease and long term effects (wanted or unwanted) of prolonged drug treatment. Long term safety studies can be open, but it is obviously of medical importance to determine how safe a drug is as compared with others of its type.
- Benefit/risk and benefit/cost analyses, where these are needed.

2. ADVERSE REACTIONS (See also Appendix 5)

It is widely considered that adverse reactions, particularly serious ones, occurring in any phase of clinical study, should be reported to national drug adverse reaction monitoring centres and not only to the manufacturer of the drug.

3. DESIGN OF STUDIES

The nature and specific uses of various study designs have been defined in many publications and will be only briefly summarized here.

Open Study: Both the patient and the doctor know which drugs are in use throughout the trial. These studies are of limited value for demonstrating efficacy, primarily because of the subjective influence on assessments.
Single Blind Study: Either the doctor or the patient knows which drugs are being used in each case. An alternative is the use of an independent (blinded) observer.

Double-blind Study: Neither patient nor doctor know which drug, active or placebo or reference, is given during the various phases of the trial. An alternative is the use of an independent (blinded) observer.

4. CONTROLS

In all comparative studies, patients should be randomly allocated to treatment or control groups; special tables for randomization are available. The randomization should take place after the patient is accepted for inclusion in the trial. Random stratification may also be required if there is wide variation in the patient material. When choosing treatment for the control groups it should be decided whether it is desirable or ethically justifiable to use a placebo or whether another active (reference) drug should be used for comparison.

Controls can in principle be of two types:

(a) Controlled trials with a parallel group: Random allocation is essential and double blind techniques should be applied.

(b) Cross-over designs in which patients serve as their own controls: Cross-over trials are mainly useful in drugs with a short half-life and/or a short duration of effect, and where the latter is reversible. If this is not the case, carry-over effects may invalidate the results; consideration should also be given to the possibility of a difference in a carry-over effect between the two drugs. The desirability or necessity for a wash-out period before entering into the trial and between the different phases in cross-over studies will depend on the carry-over effect of the drugs involved in the trial and of any drugs taken in advance.

In cross-over studies, the order of administration of drugs should be randomized since it may affect the outcome, e.g. if the first drug given produces a greater placebo effect.

Where the above-mentioned criteria for the performance of a valid cross-over trial cannot be met, preference should be given to comparative parallel between-patient studies.

Multicentre trials

These are often necessary in order to obtain a sufficient large number of patients within a short period. In a multi-centre trial, the selection of patients and collection of data are carried out by a number of physicians. The number of patients from each centre should be fairly similar. The multi-centre trial introduces certain difficulties regarding the comparability of patients as well as introducing observer differences. Multi-centre studies having a common basic trial structure, but in which each centre focuses on a different problem can be particularly useful. A project leader/trial coordinator can help to maintain cohesion between the different centres taking part in the trial.
5. USE OF PLACEBO IN CLINICAL DRUG TRIALS

The involvement of placebo in clinical trials can serve the following purposes:

1. To determine whether the experimental drug possesses any pharmacodynamic activity at all (particularly in early pilot studies).

2. In order to establish a baseline for the activity of the disease before treatment with the new drug.

3. In cross-over studies, to ensure continuity of the "treatment" during wash-out periods between two active treatments.

4. As reference preparation in trials concerning diseases for which no treatment is known.

5. As a reference in testing new drugs in disease where the effect of existing therapies is seriously in doubt.

6. As a reference in long term therapeutic studies to distinguish the actual effects of a drug on the development of disease from spontaneous fluctuations and/or improvements in the disease in question.

7. As a reference in long-term prophylactic therapies where the spontaneous course is variable and particularly where it may be influenced by several unrelated conditions.

8. As reference in diseases in which satisfactory criteria for symptom relief are difficult to establish and where a marked placebo effect is likely to be encountered.

9. To validate either a test or a method of assessment, determining to what extent the test is able to discriminate between the active drug and placebo.

Careful consideration of the ethics involved in using placebo is needed before any placebo controlled trial is designed. All measures adopted should be in accordance with the Helsinki Declaration. Very often when a placebo is involved the limitations on a study will be ethical rather than purely scientific.

6. TREATMENT SCHEDULES AND DOSAGE

The dosage schedule to be employed should be specified and explained in advance. Detailed instructions should be given. There should be a well-defined design for changes in dosage during the trial if indicated. Fixed dose increments or individual dose titrations may be necessary in the pilot studies and main clinical trials. The time of intake of the drug in relation to meals should be known and recorded. Any reference drug (used as a control) should be given at the accepted therapeutic dose; too often, reference drugs have been given in too low or too high a dose, thus invalidating the comparison as regards efficacy and safety.
7. **Measures to Monitor Compliance**

Compliance can be checked during the trial e.g. by asking the patient, by counting the remaining tablets or by monitoring plasma drug levels. The methods used should be stated in the protocol, and it is commonly advisable to employ more than one.

8. **Exclusion of Patients**

General principles applicable to the exclusion of patients (e.g. pregnant women) are as for investigations of other classes of drugs, but some special considerations may be applicable. Women of child-bearing age and patients with severe cardiovascular or renal disease should for example be excluded from studies of uricosuric agents. Women of child-bearing age and patients with liver diseases should not be given enzyme inhibitors. Elderly patients, if not excluded, should be monitored very carefully; as pointed out elsewhere in these Guidelines, there are good reasons to study "antirheumatic" drugs specifically in this class of patient.

9. **Statistical Considerations**

Statistical advice should be taken early in the planning stage of a trial:

(a) to determine the number of patients who should take part in the study in order to achieve statistically significant discrimination; the number of patients can be pre-calculated using recognized formulae;

(b) to advise on the number of patients required to demonstrate any lack of clinically relevant difference between the two methods of treatment. In that case there should be agreement between the physician and the statistician as to the power of the statistical test.
APPENDIX 2

PHARMACOKINETICS IN RELATION TO CLINICAL TRIALS
OF DRUGS USED IN RHEUMATIC DISEASES

For any new "anti-rheumatic" drug which is to enter clinical trials, information on the following matters should be either available or generated during the trials:

1. The variability in the basic kinetic parameters, both between patients and in the same patient over time.

2. The influence of physiological variables on kinetics, e.g. age, pregnancy and circadian rhythm.

3. Changing kinetics during prolonged continuous treatment (see also point 6).

4. Plasma concentration/dose ratio, variability and time taken to reach steady state.

5. Impact of disease state on kinetics, e.g. renal and hepatic insufficiency and possible influence of rheumatic disease itself.

6. Whether the kinetics demonstrate unusual features, e.g. 0-order kinetics, problematic bioavailability, high degree of first pass metabolism, slowly filled deep compartments, etc., which may influence dose policy.

7. Kinetic drug interactions. It should be possible to anticipate clinically important interactions from previous experience and monitor for them. Certain anti-rheumatic drugs interact with anti-diabetics, anti-coagulants and antibiotics.

8. Correlation between kinetic data and the effects, both therapeutic and adverse. Ideally steady state plasma concentrations should be related to clinical activity in a dose/response like manner in prospective randomized trials.

9. The pattern and effect of active metabolites which may explain apparent lack of level/effect or level/effect-time correlations.
PITFALLS, ERRORS AND PREJUDICES IN CLINICAL TRIALS

The following remarks apply particularly to studies of drugs for the treatment of rheumatic disorders, but many of them are clearly relevant to any clinical trial. More detailed consideration of many of the points summarized here will be found elsewhere in these Guidelines.

Before agreeing to undertake a trial, an investigator should carefully consider the following questions:

1. Are the basic studies (i.e. animal experiments to determine acute and chronic toxicity) adequate and conclusive?

2. In which phase of study is the preparation at present? Is the optimal daily dose already established? How advanced and conclusive are human pharmacological studies?

3. Does earlier human work justify continuation?

4. Are the trial objectives clearly defined? Usually a given trial can answer only one main question; for example, the best trial design for assessing efficacy is not necessarily the best for assessing safety and vice versa. For each trial, main and subsidiary objectives should be divided.

5. Is the objective of the trial fitted to answer a clinically relevant question? For example, a trial including 6 different "pure" analgesics performed in rheumatoid arthritis without NSAID does not answer the question whether such an analgesic is able to further reduce pain in patients already receiving anti-inflammatory treatment.

6. Is an appropriate trial design proposed? Options are given in Appendix 1.

An open trial has very severe limitations but is not necessarily invalid or obsolete for all purposes and can for example be the best method of identifying late adverse reactions to a drug.

On the other hand, a cross over study is pointless in acute gout and useless for assessing a DMARD in RA because of the irregular and unpredictable course of this disease.

7. Is the population entering the trial correctly selected, i.e. what are the criteria for inclusion, in particular the diagnostic criteria? What are the criteria for exclusion? Has the authoritative literature been followed on these points?

8. Are the trial patients representative? Is patient selection sufficiently broad? The patients studied should at least represent a defined subgroup of the whole patient population.
9. If a wash-out period is planned, is it of the right length? If it is long one (i.e. several days), there is a risk of a selection bias towards patients with less pain who are therefore more able to endure several days without drug treatment. A short wash-out period may be insufficient to serve its purpose.

10. Is there true randomization for (1) the order of drug or placebo administration in the cross-over design or (2) enlistment in one of the parallel groups? Is randomization performed in a valid manner?

11. Comparability. When comparing parallel groups the number of patients included should be sufficient to allow for stratification of relevant population characteristics in each group. If a comparative study is planned with one or several reference drugs as controls, has the optimum daily dose of each been chosen?

12. Was expert statistical advice taken on the trial design and number of patients? What kind of statistical tests are recommended? Is the power of such tests enough to reach a meaningful answer? Was the advice followed?

13. Is the choice of assessment measures and the number of such measures appropriate? Use of too many is unnecessary and tedious; use of too few leads to meaningless results).

14. In multi-centre trials are the measurements to be used in assessment well standardized and familiar to every investigator?

15. What is the risk of a double-blind being broken? Some reference drugs have characteristic side effects (for example, headaches with indomethacin or loss of taste with penicillamine) which make them easily recognizable.

16. How are adverse reactions to be recognized? A neutral question (e.g. how does the medicine suit you?) will tend to produce more reliable results than a leading question.

17. Is the assessment form for recording observations already finalized or still subject to alteration? A good lay out for recording observations is best designed with the cooperative efforts of the physician, statistician and other investigators involved in the trial. The presentation should be clear and unequivocal.

18. How is compliance to be checked? By asking the patient? By checking blood or urine levels? By counting the number of tablets returned by the patient when attending for assessment?

19. Last but not least, is the trial ethically acceptable? Matters which raise doubts on this score can include:

   (a) withdrawal of much-needed therapy over long periods;
   (b) performance of scientifically invalid studies, e.g., merely for promotional purposes;
   (c) failure to provide for continued treatment, if this has proven to be beneficial, after the trial has ended.
APPENDIX 4

RHEUMATOID ARTHRITIS; PRESENT STATE OF KNOWLEDGE

WITH RESPECT TO DRUG TREATMENT

I. Non-steroidal anti-inflammatory drugs (NSAID) in rheumatoid arthritis

As compared with placebo, NSAID exert a moderate suppressive effect on the clinical signs of synovitis in rheumatoid arthritis, i.e. joint pain, swelling, tenderness and stiffness. The drugs have no convincing effect on the general signs of disease activity, including anemia and alterations in acute phase reactants, and it is doubtful whether they influence the titre of Rheumatoid Factor or ANA. The number of valid, relevant studies is, however, small. At present there is no evidence that treatment with NSAID influences the development of bone erosions, but there is a lack of controlled trials; if present this effect is at best only slight. The clinical efficacy of the various types of NSAID appears to be rather similar if the drugs are given in comparable doses. Some individual differences in the sensitivity to therapeutic effects may exist but the evidence is sparse. The major value of the existence of a number of different NSAID is the variation in patient tolerance to individual drugs when treated with full therapeutic doses.

II. Disease-modifying antirheumatic drugs (DMARD) in rheumatoid arthritis

These drugs include:

1. Anti-malarials (notably chloroquine)
2. Gold salts
3. Penicillamine and other sulphydryl compounds
4. Cytostatic and immunosuppressive drugs: (azathioprine, cyclophosphamide, chlorambucil, methotrexate)
5. Miscellaneous drugs (levamisole, dapsone, cyclosporin, sulphasalazine etc.)

All the DMARD may produce remission in 30-70 per cent of patients with rheumatoid arthritis but relapse is common after withdrawal. During treatment the clinical signs of synovitis decrease - as do the generalized manifestations of inflammation. Some authors have suggested that certain DMARD may retard the development of bone erosions in particular patients, but there may be progression of bone erosions in spite of improvement in the clinical symptoms. There are no studies which demonstrate any influence on the late clinical outcome in RA, and to this extent the term "disease modifying drugs" is a misnomer.

Up to 1982 a total of 83 controlled trials had been reported (Halberg, 1984), comprising variously:

1. DMARD versus placebo (40 studies)
2. DMARD versus NSAID (1 study)
3. One type of DMARD versus a different type of DMARD (20 studies).
4. The same DMARD at different dose levels (22 studies).
In most of the controlled trials extending beyond one year and a half there is a 50 to 70% drop-out of patients, due to lack of effect or due to side-effects. This high drop-out rate, alongside the unproven validity of measures, make it difficult to interpret the results of much published work in this field.

The most frequently used variables in 46 of the above studies in which one treatment group differed from another by at least one variable were in order of decreasing frequency as follows:

Grip strength, ESR, morning stiffness, rheumatoid factor titre, Hgb, articular index (Richie, Lansbury), morning stiffness, number of tender joints, functional class (ARA), patient's estimate, PIP circumference, walking time, number of swollen joints, observer's estimate, total joint count (tender and swollen joints), NSAID consumption, glucocorticoid consumption, isotope index.

Joint tenderness and swelling, morning stiffness and patient's estimate seemed to be relatively sensitive. In general clinical measures appeared to be more sensitive than laboratory variables, but further validation of many of these is required for future work.

III. Glucocorticosteroids in rheumatoid arthritis

Glucocorticosteroids are powerful anti-inflammatory drugs. The effect appears rapidly in the course of hours or days. There is, however, no evidence that glucocorticosteroids improve the final outcome of rheumatoid arthritis; on the contrary, the severe side-effects from long-term treatment may amount to adding a new chronic disorder to the patient's existing disease.

Much of the published clinical work dates from an earlier period and is now regarded as unsatisfactory.

IV. Questions requiring further study with antirheumatic drugs

The present state of knowledge with respect to antirheumatic drugs must be regarded as unsatisfactory, and some of the matters particularly in need of investigation are listed below.

(a) General
1. Mechanisms of action
2. Effect of combined treatment using drugs from various groupos
3. Validation of methods to measure long-term outcome
4. Effect on the long-term outcome of the disease
5. Benefit/risk ratio

(b) For NSAID:

Optimal dosage schedule (number of daily doses, relationsup to circadian rhythms and meals).
(c) For DMARD

1. Effect of early treatment on long-term outcome

2. Correlation between improvement of clinical signs or synovitis and the development of bone erosions

3. Effect of long-term treatment on bone erosions and final outcome, i.e. importance of maintenance therapy

(d) For glucocorticosteroids

Optimal dosage schedule (e.g. value of intermittent high dose therapy).
ADVERSE REACTIONS TO DRUGS USED IN THE TREATMENT OF RHEUMATIC DISEASES

Introduction

Adverse reactions to antirheumatic drugs are numerous and varied. The interpretation of adverse reaction reports may be influenced by a number of possible confounding factors e.g. polypharmacy, lack of compliance, taking of non-prescribed drugs, influence of disease state and/or immunogenetic status. Causality is difficult to establish unless re-challenge with the suspect drug can be justified ethically. Risks associated with the use of drug must be seen in the context of the seriousness of the disease to be treated and the expected benefit to the patient from the drug in question. Sub-groups of patients that require particular attention include the very young, the very old, women who are of child bearing potential and those with diseases likely to affect drug metabolism.

NSAID

Gastrointestinal tract irritation is the most characteristic adverse effect associated with the use of NSAID. Bronchospasm may be precipitated in patients suffering from, or with a previous history of, asthma or other allergic disease. Most of the NSAIDs interact with anticoagulants which may necessitate adjustment of the anticoagulant dose. Certain of the NSAIDs also interact with hydantoins, hypoglycemics, sulphonamides and probenecid. The possibility that a drug may interfere with the results of laboratory investigations should be borne in mind.

Although many adverse reactions are common to all NSAID, their incidence can vary. In addition, some newer molecules have moved sufficiently far away from the traditional pattern to introduce new effects; even in this supposedly familiar field, the investigator should always be on the lookout for the unexpected.

DMARD and immunomodulators

These drugs have all been associated with serious and occasionally fatal adverse reactions e.g. blood dyscrasias, renal and hepatic toxicity - appropriate monitoring is therefore mandatory. Cytostatic/immunosuppressive drugs may also be associated with an increased incidence of malignancy which may not occur until some years after drug exposure.

Sources of information


Other sources of information include national and international reporting systems, drug data sheets, reports in the medical literature and personal communications from medical colleagues.
SELECTED LITERATURE


CONSTITUTION OF THE WORKING GROUP

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Definitive texts

Guidelines for the Clinical Investigation of Antihypertensive Agents (1977)
(Document not numbered; see also draft for a revised version, below)

No. 1 Guidelines for the Clinical Investigation of Anxiolytic Drugs (1983)

No. 2 Guidelines for the Clinical Investigation of Hypnotic Drugs (1983)

No. 3 Guidelines for the Clinical Investigation of Antidepressant Drugs (1984)

No. 4 Guidelines for the Clinical Investigation of Antiglaucomatous Drugs (1984)

No. 5 Guidelines for the Clinical Investigation of Drugs Used in the Treatment of Rheumatic Diseases (1985)

Revised draft texts

- Guidelines for the Clinical Investigation of Anti-arrhythmic Drugs (1983)


- Guidelines for the Clinical Investigation of Neuroleptic Drugs (1983)

- Guidelines for the Clinical Investigation of Antihypertensive Drugs (1985)

Other draft texts

- Standards for the Selection of Parenteral Fluids

Index to Guidelines

Drug Regulatory Index No. 1 (2nd revised edition): Index to Guidelines for the Clinical Investigation of Drugs - January 1985 (an index to clinical guidelines issued by national, regional and international bodies throughout the world)

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