

Studies of drugs and other measures to prevent and treat osteoporosis; a brief guide

Prepared by John D Wark and Ann Westmore

This guide aims to provide :

- **An improved understanding of important features of osteoporosis and of well- conducted research on it**
- **Relevant information about the laboratory and animal research that ideally underpins human (clinical) trials in osteoporosis**
- **An awareness of the sequence of laboratory, animal and human studies used to provide valid answers to research questions**
- **Background information for considering participation in a clinical trial of a drug or other measure targeted at preventing or treating osteoporosis**

As you will see, this guide is intended for people who wish to learn some key points about the testing of drugs and other measures to prevent and treat osteoporosis. There is also a more detailed booklet available if you wish to know more. It is entitled “Studies of drugs and other measures to prevent and treat osteoporosis; a guide for non-experts”.

Bone

Bone is a hardened mass of living tissue that supports the body and protects internal organs from injury. In adults, there is a continuing process of bone renewal in which small amounts of bone are broken down (bone resorption) and replaced by new bone (bone formation). Within bone, the marrow produces large numbers of blood cells. Importantly bone is also an essential reservoir of minerals for the body.

Osteoporosis

The genetic makeup of individuals, ageing, the menopause in women, and other factors affecting both men and women are associated with changes to the structure and function of the body, one of which is a reduction in the strength of bone.

Osteoporosis is diagnosed when the loss of bone density and strength leads to an unacceptably high tendency for bones to fracture (that is, to break).

Bone density has been divided by the World Health Organization into four levels:

- Normal
- Low bone mass (osteopenia)
- Osteoporosis in which fractures have not yet occurred
- Severe or established osteoporosis (when fractures have occurred due to bone fragility)

About Osteoporosis

In most countries people are living longer and there are correspondingly more cases of osteoporosis. Even after taking account of this trend in population ageing, there is evidence of increasing fracture rates in some parts of the world. This translates into more osteoporosis-related disability, pain, deformity, dependence and even death. Reassuringly, osteoporosis prevention, early detection and treatment are capable of reducing these negatives.

Although the problem of osteoporosis is shared by ageing men, in most western countries the risk of the condition is about twice as high in women, with approximately 40% of women over 60 years of age being affected. The higher incidence of osteoporosis in women reflects, in part, their tendency to live longer than men as well as the occurrence of a period of accelerated bone loss around the time of, and for some years following, the menopause. Indeed, because of women's higher risk and longer lifespan, there are 3-4 times more hip fracture cases in women than in men

Research on osteoporosis

What can it offer?

Researchers studying osteoporosis have concentrated their efforts in several main areas:

- Understanding the basic biology of bone
- Studying the relationship of bone quantity and quality to fracture risk
- Examining other factors that predict a high risk of developing osteoporosis.
- Studying measures that decrease the risk of fractures and associated ill-health and death

Potential new treatments are tested in the laboratory and in animals (preclinical research), before being given to humans.

Basic (laboratory) studies

Studies performed in tissue culture laboratories can provide useful insights into how many test agents work. However, with current knowledge, these experiments cannot replace animal studies because bone as an organ, together with the complex mechanisms controlling it, cannot be mimicked in the laboratory.

There are two main types of osteoporosis-related laboratory research:

- i) studies of bone resorption (breakdown)
- ii) studies of bone formation

Preclinical studies

What are preclinical studies?

Before embarking on human testing, research is usually conducted in animals to assess the safety and potential usefulness of a proposed intervention (that is, a means of prevention or treatment of the disorder). Such studies are described as preclinical.

Why we need animal studies:

- to gain initial evidence that an agent is safe to administer to humans
- to establish how a proposed intervention affects the mineral content, mass or strength of bone, thus providing grounds for its use in humans
- to show that the proposed intervention can be effective in animals that show features of osteoporosis as it occurs in humans
- to clarify whether exposure to the intervention results in the formation of good quality bone
- to shorten the time required to screen for potentially useful treatment agents
- to gain insights into the way in which an intervention influences bone.

Clinical trials

A clinical trial is any systematic study of a drug or other intervention in patients or non-patient volunteers.

This guide refers mainly to pharmaceutical (drug) interventions for preventing, stabilising or treating osteoporosis. However, much of the discussion is also appropriate for the assessment of non-drug measures, such as the use of hip-protecting devices in the elderly and physical activity in all age groups.

Bone density as a “surrogate” (substitute) for fracture risk

Measurement of bone mineral content (bone density or bone mass) has a central place in osteoporosis research and the assessment of preventive or treatment interventions.

In principle, any of the well-established bone density measurement techniques is usable in clinical trials of osteoporosis provided that characteristics like reliability and interpretation are taken into account. In general, bone density should be measured at two or more bone sites, one of which should be the spine or hip. Most of these techniques determine the amount of mineral in bone by measuring the absorption of a beam of radiation by the presence of mineral-containing tissue in the beam's path. Small amounts of radiation are used, most often in the form of x-rays.

Fracture assessment and height

All fractures that a subject has suffered before entering a clinical trial should be recorded. Once a trial has started, details of any other fractures occurring should be documented with information on when and how they happened. Measurements of vertebral bone dimensions are needed to assess the occurrence of spinal fractures.

An additional informative way of assessing an intervention's effect on spinal fracture occurrence is to monitor differences in the heights of individuals in treatment and control groups.

Quality of life and other measurements

Decreased illness and improvement in quality of life are what anti-fracture interventions ultimately aim to achieve. Improved ways to measure quality of life are under development.

Clinical trial methods; general principles

The protocol

Every clinical trial should be carried out in accordance with a protocol, that is a document stating the background, rationale and objectives of the trial and that describes its design, methodology and organisation, including statistical considerations, and the conditions under which it is to be performed and managed.

The protocol should state the reasons why the trial should be undertaken in humans; the nature and degree of any known risks; the groups from which it is proposed that trial subjects will be selected; and the means for ensuring that they are adequately informed before they give their consent to participate. It should receive scientific and ethical appraisal by one or more review bodies (such as an institutional review board, ethics committee, drug regulatory authority), constituted appropriately and independent of the investigators and the source of funding.

The protocol should include a description of the end-points, that is, criteria that can be measured to assess whether an intervention has been effective.

The design of clinical trials

Many trials are randomized and placebo-controlled.

Randomisation

This is the random assignment (that is, like picking numbers out of a hat) of research volunteers to treatment and control groups, or to different treatment groups. It helps the statistician to separate the effect of a treatment from other differences found among people in any group. Randomisation helps in calculating the likelihood that the difference seen in an experiment is due to an effect of the treatment rather than to chance. When we randomise, we are more likely to end up with groups that are similar in terms of all these chance effects and so bias (recognised or unrecognised) is minimised.

A *control group* is a comparison group intended to be similar to the treatment except in not receiving the treatment under study.

A *placebo* is a harmless inactive substance which is given to the control group instead of a biologically active agent to help separate the effects of the agent from other influences related to participation in the trial. The use of a placebo means that the involvement of the control group in the trial can mimic the actively-treated group in all respects except that the control group does not receive the treatment being tested.

In many clinical trials, all participants are given an active agent (usually calcium tablets) in addition to the placebo or test agent.

Blinding

It is important that, where possible, researchers and others dealing with the different patient groups in a trial are not aware which patients are receiving an active intervention and which are receiving a placebo. This is referred to as *blinding* of the research team. Blinding is important to ensure that the researchers do not (subconsciously) deal with some subjects or their results differently because of the treatment the subjects are receiving. Where possible, the trial participants also should be blinded, that is, unaware during the trial whether they are receiving the intervention or placebo. When the researchers and the trial subjects both are unaware of who is receiving active and placebo agents, the trial is described as *double-blind*.

Duration of studies

Virtually all the interventions investigated to date to prevent, minimise or reverse human bone loss induce initial changes in bone mass that take around two years to reach a steady state, that is, a new balance between bone gain and loss. This is an important reason for continuing clinical trials of bone therapies for several years at least. In addition, at least several years of observation are needed to detect meaningful changes in the rate of fracture.

Safety issues

Tools for investigating safety aspects include studies of how drugs are processed in the body, evaluation of blood counts, tests of kidney and liver function, blood calcium and phosphate levels and, in some circumstances, bone sampling.

There should be provision for analysing the safety and effectiveness of the study intervention at least annually during a trial without revealing to participants and investigators details of the response to intervention. Rules should be established for every trial to ensure that this monitoring procedure will detect an unacceptable hazard to participants and that the trial will be stopped in such an event.

The size of a trial should be sufficient to adequately assess the safety of an agent in relation to its likely benefit to a target population. The lower the risk of fractures in a population, the greater is the need to demonstrate the safety of an intervention by studying large numbers of subjects (that is, to show that there is a favourable benefit-to-risk ratio).

Researchers also should take account of potential hazards of techniques. For example, bone density tests such as SPA, DPA, SXA and DXA use very small amounts of radiation and may be acceptable for children but computed tomography (CT) has a higher radiation dose and may not be suitable in a research setting.

Good clinical practice

Researchers should consult the guidelines for good clinical practice for trials on pharmaceutical products (World Health Organisation, 1995).

Phases of clinical drug development

The clinical development of a drug progresses through several steps or phases allowing the short-term safety, chemical processing and excretion by the body, the way the drug works, its efficacy, long-term safety and overall therapeutic usefulness to be evaluated in an appropriate sequence.

i) Phase I studies

The first study of a new pharmaceutical agent (drug) or new drug formulation in humans is known as a Phase I study. Its principal aim is to ensure the agent or formulation is safe and well-tolerated. Other aims are to gain an outline of how the agent or formulation acts in the body and the way the body processes and excretes it. This type of information helps in predicting whether people in ill-health (with conditions such as kidney or liver disease) will experience adverse effects as their bodies attempt to handle the agent. Preclinical (animal) findings should be used as a guide in designing these studies.

Phase I studies on bone-active agents are generally carried out in small numbers of healthy volunteers. However, it may be appropriate to include patients with osteoporosis, for example, where the agent is known to persist in the body for a very long time.

Phase II, III and IV studies may involve research volunteers with or without osteoporosis, depending upon whether the aim is to study treatment or prevention of osteoporosis, respectively.

ii) Phase II studies

The purpose of a phase II study is to demonstrate that the agent being tested has a beneficial effect and is safe for short-term use in patients suffering from a disease or condition which the agent is intended to counter.

A further aim of phase II studies is to explore a range of possible dosages and their effects. In so doing, it is hoped to identify a dose which provides a beneficial treatment effect and which is also well-tolerated by patients. Phase II studies involve a limited number of participants.

iii) Phase III studies

These are trials in large numbers of subjects with the purpose of determining the short- and long-term safety and effectiveness of a drug preparation and of assessing its usefulness as a treatment.

Confirmation of effectiveness requires supporting evidence from at least two well-designed studies. Assessments of safety require a careful analysis of the number of participants studied, their state of health and their duration of exposure to the test agent. The circumstances of studying test agents should be as close as possible to normal conditions of use.

iv) Phase IV studies

These studies are carried out on the basis of the product characteristics for which marketing of a drug has already been approved. They include post-marketing surveillance (for example, monitoring for adverse effects) and further assessment of how a drug is used in clinical practice and of its overall usefulness.

Phase IV studies are particularly important because agents used to prevent or treat osteoporosis are commonly prescribed for a long time and, even after treatment ends, they may be retained in bone for many additional years. Such studies are performed to further demonstrate the intervention's safety and the persistence of its beneficial effects. Approaches to re-introducing the treatment also may be studied in phase IV.

Most phase IV studies should include a control group. An exception sometimes arises when safety issues are being addressed and the main aim is to estimate the occurrence of adverse effects.