Guidelines for preclinical evaluation and clinical trials in osteoporosis

World Health Organization
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Contents

1.
Introduction

Osteoporosis and associated fractures increase markedly with age and are a major cause of mortality and morbidity — and thus of medical expense — throughout the world. The frequency of osteoporotic fractures is much higher in women than in men because of their generally greater life-expectancy and because of postmenopausal hormonal changes, and it has been estimated that the number of women over the age of 65 years will increase from 188 million in 1990 to 325 million in 2015.

Because of the increasing importance of osteoporosis, consensus is needed on the principles and methods applied in clinical trials of the efficacy and safety of drug treatments for the disease. A number of scientific groups and drug regulatory authorities have produced guideline documents and position papers on the criteria to be applied in investigations and evaluations of new treatments. The focus of these documents has varied, but none has provided a comprehensive statement of guiding principles for the design, implementation, and interpretation of either preclinical testing or clinical trials in osteoporosis.

To address this need, WHO's Division of Drug Management and Policies established a working group in 1995; the group included drug regulators and scientists and was charged with the development of international guidelines. It was recognized that such guidelines should:

- comprise evidence-based principles rather than detailed prescriptions for the conduct of studies;
- be sufficiently broad in scope to encompass the various types of osteoporosis, and their prevention and treatment (including non-pharmacological interventions);
- be relevant to all those who are involved in the development and evaluation of interventions, e.g. the pharmaceutical industry, drug regulatory authorities, and individual scientists.

The group identified a need for studies in different populations (men, children, premenopausal women, etc.). A recommendation for the development of further guidelines is given in the annex to this publication.

In developing the present guidelines as a practical tool for use by WHO Member States, every effort has been made to ensure their compatibility with

existing national and other provisions and to provide a framework on which national guidelines may subsequently be based. The guidelines have been reviewed by internationally accredited experts, by drug regulatory authorities, and by the pharmaceutical industry.

2.
Background

Osteoporosis is a major health-care problem of ageing communities yet, until recently, it has received relatively little attention. Its clinical significance lies in the fractures that arise, most commonly of the forearm, the vertebral bodies, and the hip. Of these, the most serious is hip fracture because of the high morbidity and associated mortality — and consequent high cost to health services (*1*). Vertebral, forearm, and upper humeral fractures also cause considerable morbidity and, since they tend to occur in younger individuals than hip fractures, have significant long-term impact on quality of life. Fractures at many other sites are also more frequent in osteoporosis than in health, but these are less important.

In most countries the incidence of osteoporosis is about 2–4 times higher in women than in men; this is related to the loss of bone that occurs as a result of estrogen deficiency after the menopause. In addition, women generally live longer than men, so that the frequency of osteoporotic fractures in most communities is at least 3 times higher in women than in men.

The absolute risk of osteoporosis varies between countries, and is highest in North America and western European countries. At the age of 50 years the remaining life-time risk of hip fracture in white women from the United States is 17.5%, and similar levels of risk are found in most Western European countries. Estimates for other types of osteoporotic fracture, such as vertebral and Colles fracture, are nearly as high, so that the combined total risk for fracture due to osteoporosis is about 35%. These figures are conservative since they take account only of the vertebral fractures that come to clinical attention and no account of osteoporotic fractures at other sites. The risks for osteoporotic fractures in both men and women are lower in other geographical areas, including Africa and Asia, but are likely to increase markedly in the future.

Between 1.3 and 1.6 million hip fractures were estimated to have occurred worldwide in 1990. These numbers will rise significantly as the number of elderly people increases because of continued improvements in life-expectancy. Between 1990 and 2025 the number of men aged 50 years or more will increase by 150% in Europe and by more than 200% in all other regions. The greatest increments will occur in Africa, Asia, and Latin America. For women the predicted increases are 131–140% in Europe, 183% in North America, and

more than 200% in all other regions. Asia will have the highest absolute increase in the elderly because of the large present population of the region. These demographic changes suggest that, by the year 2025, the number of hip fractures will have increased to 4 million per year worldwide, with the largest number occurring in Asia.

It is very likely that these predictions represent an underestimate since the age- and sex-specific incidence of osteoporotic fractures is increasing in both men and women, particularly in Asia. With even modest assumptions concerning the secular trend, the number of hip fractures in 2025 could be as high as 6 million, so that osteoporosis has a substantial and ever-increasing economic significance.

Treatment and prevention of osteoporosis — and even attitudes to the problem — vary widely from country to country, despite both the importance of the disease and improved knowledge of its causes. This is largely the result of a lack of awareness among medical practitioners and health ministries of the objectives and effects of interventions in osteoporosis. The rapidity with which new treatments and technologies have developed has proved a further obstacle to a cohesive and rational approach to the problem. There is thus a pressing need for consensus, based on the most scientifically appropriate information, concerning the manner of assessing the efficacy of therapeutic regimens.

Several national and international guidelines and position papers have been developed in recent years (*2–8*). While these have differed in their emphasis, they have focused principally on women with postmenopausal osteoporosis and have not considered other forms of osteoporosis. Differences in substance relate to uncertainties in the relationship between bone mineral density and fracture outcome. Considerable recent experience in osteoporosis studies using both bone mineral assessments and fractures has helped to clarify this relationship. Use of animal models of bone strength, rather than of osteoporosis, has also resolved some of the uncertainties (*9*), allowing more cohesive views and strategies to be developed.

3.

Definition of osteoporosis and related terms

3.1 Conceptual definition of osteoporosis

Various definitions of osteoporosis have been offered to describe the outcome of events (fragility fractures), the process giving rise to porous bones, or the resultant diminution in bone mass. The following definition (*10*) is now generally accepted:

"*A disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.*"

While recognizing the multifactorial nature of the events that give rise to fractures, this definition also embraces the concept that low bone mineral density is an important component of fracture risk. Since bone mineral content or density can be determined with precision and accuracy, its measurement forms the basis for an operational definition of osteoporosis.

3.2 Operational definition of osteoporosis

The relationship between bone mineral density and fracture risk is continuous, and an estimate of bone mineral density therefore provides an effective assessment of fracture risk. It is thus possible to choose a value for bone mineral density that defines the presence of osteoporosis.

Bone mineral content or density in young healthy women ("peak bone mass") is normally distributed, irrespective of the measurement technique used. By virtue of this normal distribution, bone density values in individuals may be expressed in relation to a reference population in standard deviation (SD) units; this reduces the problems associated with calibration differences between instruments. Use of standard deviation units in relation to the young healthy population is referred to as the t-score, where the mean is ascribed a value of zero.

The World Health Organization has proposed two diagnostic thresholds of bone mineral density for Caucasian women, based on the distribution of skeletal mass in young healthy individuals; these thresholds permit the establishment of four general diagnostic categories (*1*):

- *Normal.* A value for bone mineral within 1 SD of the young adult reference mean (t-score $\geqslant -1.0$).

- *Low bone mass (osteopenia).* A value for bone mineral more than 1 SD below the young adult mean but less than 2.5 SD below this value ($-1.0 >$ t-score > -2.5).
- *Osteoporosis.* A value for bone mineral 2.5 SD or more below the young adult mean (t-score $\leqslant -2.5$).
- *Severe (established) osteoporosis.* A value for bone mineral 2.5 SD or more below the young adult mean in the presence of one or more fragility fractures.

Suitable diagnostic cut-off values for non-Caucasian women and for men are less secure. It has been suggested (*1*) that a similar absolute value for bone mineral density to that used in women can be taken as a cut-off point for the diagnosis of osteoporosis in men — that is, a value 2.5 SD below the average for adult premenopausal women. It should be recognized that cut-off values are arbitrary and may differ according to sites measured, age, and type of equipment.

3.3 Intervention thresholds

An intervention threshold depends upon absolute risk and upon the risks and benefits of a particular treatment, and should be distinguished from a diagnostic threshold.

3.4 Intervention categories

Four intervention categories are defined below. Although such definitions and thresholds are inevitably arbitrary, they enable the objectives and categories of treatment to be more closely defined.

- *Prevention:* defined as an intervention in individuals with normal skeletal status or as a global intervention in the community. Examples include regimens that modulate peak bone mass and contribute to its preservation, and agents that prevent bone loss or preserve skeletal architecture in individuals at risk.
- *Prevention of osteoporosis in patients with osteopenia:* defined as intervention in patients with low bone mass (osteopenia), but without osteoporosis. Its aims are to prevent osteoporosis and reduce the probability of future fractures.
- *Treatment of osteoporosis:* defined as intervention in patients with osteoporosis. Its aims are to reduce the probability of fractures.
- *Treatment of severe (established) osteoporosis:* defined as intervention in patients who have sustained one or more fragility fractures associated with osteoporosis. Its aims are to reduce both the risk of further fractures and the morbidity associated with fracture.

Alternative intervention categories may be based on stratification of other risk factors for fractures, for example biochemical markers of bone turnover, hip axis length, family history of fractures, and the risk of falls.

4.
Preclinical studies

4.1 Introduction and aims

Preclinical evaluation is an essential component of the development of pharmaceutical interventions for osteoporosis. A similar systematic approach can also be used, at least in part, for interventions of a nutritional or mechanical nature. The general aims of preclinical evaluation fall into two categories — those relating to the general description, metabolism, pharmacodynamics, safety, and toxicity of any new agent, and those relating specifically to bone metabolism.

The aims of preclinical studies specifically relating to osteoporosis are:

(a) To establish the relationship between the effects of an intervention on bone mass and on bone strength. In particular, studies should identify whether the use of an agent capable of restoring or preserving bone mass is associated with the formation of new bone tissue with normal architecture, and — particularly — with a commensurate increase in bone strength.
(b) To elucidate the mechanism of action of a pharmaceutical agent and thus provide the rationale for its use in humans.
(c) To demonstrate effects in animal studies of osteoporosis.
(d) To establish the effects of long-term exposure to the agent on the quality of skeletal tissue.
(e) To examine the effects of intervention on fracture repair.

The results of preclinical evaluation will determine whether a new agent should be tested in humans and, if so, the population and the end-points required for phase I, phase II, and phase III of the evaluation process.

Consensus is still lacking within the scientific community and drug regulatory authorities on a completely satisfactory experimental model (or models) for human osteoporosis because any existing models that display all the typical features of osteoporosis still fail to display the **same** pattern of spontaneous fragility fractures. However, several animal models of osteoporosis as defined in section 3.1 are available or under development.

Features of osteoporosis include low bone mass, microarchitectural deterioration of bone tissue, and increased bone fragility. Animal models are

available for estrogen-deficiency osteoporosis and for other less common forms of the disorder (e.g. due to corticosteroids or immobilization); indeed, depending on the species and type of intervention, animal models can reproduce more or less all the characteristics of osteoporosis.

The primary objective of preclinical testing is to investigate the pharmacodynamic effects and, in particular, the biomechanical consequences of a putative therapeutic intervention. Precise and accurate techniques, often comparable to those used in clinical evaluation, are available for assessing drug-related effects at clinically appropriate sites. These techniques include the measurement of bone mass and bone mineral density, evaluation of microarchitecture, and determination of static and dynamic histomorphometric variables, biochemical indices of skeletal turnover, and, most importantly, bone strength under well controlled conditions.

For some therapeutic interventions, there is increasing evidence that the results of preclinical studies can predict whether changes in bone mass will be associated with modifications in bone fragility — and therefore in fracture rate — in osteoporotic patients. For other therapeutic agents, however, the predictive value of these models is less secure.

The crucial importance of preclinical evaluation is underscored by the limited number of validated non-invasive techniques for assessing bone strength in humans. Assessment is best achieved by measurement of fracture rates. However, evaluation of fracture rates in phase III studies poses a number of difficulties relating to the multifactorial nature of fracture, the large sample sizes required (particularly for hip fracture), and uncertainties concerning the definition of incident vertebral fractures (i.e. fractures occurring during the study). It is therefore recommended that preclinical and clinical programmes for assessing the efficacy of therapeutic interventions be complementary. A comprehensive and adequate preclinical programme is therefore expected to reduce the requirements of clinical studies. Factors that may influence the clinical programme include the appropriate choice of preclinical models, and also the findings relating to the mechanism of action and general properties of the agent tested (see section 5.2).

4.2 Studies *in vitro*

Studies *in vitro* should complement a programme of *in-vivo* investigations with the aim of identifying or specifying the mode of action of the test intervention. There are several *in-vitro* models that can be used to assess the effects of interventions on bone resorption and, to a lesser extent, on bone formation.

4.2.1 Studies on bone resorption

Bone tissue culture systems using fetal mouse calvaria or long bones can provide information on the effects and dose characteristics of agents that inhibit bone resorption. These systems provide the opportunity to establish the

correspondence between characteristics determined *in vivo* and *in vitro*. They also allow assessment of the effects of the way in which interventions affect systemic and local factors that directly influence bone resorption. At the cellular level, appropriate experimental systems are also available that permit the effects of agents on osteoclast formation and activity to be determined.

4.2.2 Studies on bone formation

Tissue and cell culture systems can be used to explore the mechanism of action of agents shown to stimulate bone formation *in vivo*. Various transformed or non-transformed animal or human osteoblast-like cells can be used to test effects of the agent on proliferation, differentiation, and cell phenotype, and to identify cellular transduction signalling mechanisms. Generally speaking, *in-vitro* studies of bone formation are less well characterized in terms of their applicability to *in-vivo* situations than is the case for agents acting primarily on bone resorption. Moreover, there are no widely validated *in-vitro* systems for examining the effects of therapeutic agents on formation and mineralization of lamellar bone.

4.3 Animal models

Animal models should be appropriate for the intended clinical application. For drugs intended to prevent or reverse postmenopausal osteoporosis, a model should have at least the following characteristics:

- increased bone turnover after oophorectomy;
- bone loss leading to an osteoporotic state that is not spontaneously reversible;
- bone loss affecting both cortical and cancellous tissue at relevant skeletal sites such as the vertebral body, femoral neck, metaphyses and diaphyses of long bones; and
- increased skeletal fragility.

4.3.1 Animal species

Preclinical studies may be carried out in various species including mice, rats, rabbits, mini-pigs, sheep, dogs, and monkeys. The choice of species depends partly on the histodynamic characteristics of basal bone remodelling patterns and their comparability to those observed in humans, and partly on their responsivity to calciotropic and osteotropic stimuli or to the interventions, and the extent to which they are predictive of the response in humans. In addition, for some forms of osteoporosis, such as those caused by corticosteroids and immobilization, satisfactory models are more species-specific than is the case for hypogonadal states. Other factors that determine the choice of model include the consistency and rapidity of bone loss at various skeletal sites,

availability of animals and the ease and safety of their handling, and cultural sensitivities, which may preclude the use of particular species in some countries.

4.3.2 Experimental techniques

Various techniques may be used to induce changes in bone mass in experimental animals. These include oophorectomy, orchidectomy, corticosteroid use, manipulation of dietary calcium intake in lactating and non-lactating animals, immobilization by using plaster-casts, hemicordectomy, and sciatic denervation.

Use of these experimental animal models for documentation of drug effects is an important component of the initial assessment of efficacy and safety. For example, the results of several therapeutic interventions in the oophorectomized adult rat mimic observations made in postmenopausal osteoporotic women.

Newer models of osteoporosis, though less well characterized, are worthy of consideration. Some rodent strains, for instance, have low peak bone mass or display spontaneous signs of osteoporosis associated with accelerated ageing.

Apart from models of human osteoporosis, several other experimental *in-vivo* systems are appropriate for selecting molecules of potential interest and for dose-finding. This has been particularly well validated in establishing the potency of anti-resorbing drugs and their propensity to inhibit the mineralization of bone. Such models are also suitable for determining the potency of therapeutic interventions in animals treated with agents that enhance bone resorption.

Intercurrent fractures are common in patients with osteoporosis, and their repair may be affected by interventions. For this reason experimental models of fracture healing are considered to be important for preclinical evaluation.

4.3.3 End-points

A series of relevant end-points can be evaluated using either invasive or non-invasive techniques. These techniques include histomorphometry, *ex-vivo* culture of bone-forming or bone-resorbing cells, the chemistry and biochemistry of bone tissue, assessment of biochemical indices of skeletal turnover in blood and urine, assessment of metabolic balance of calcium combined with radioactive calcium kinetics, radiogrammetry of bone radiographs, neutron activation for whole-body calcium, single- and dual-energy absorptiometry, quantitative computed tomography, and dual-energy X-ray absorptiometry.

The change in resistance to mechanical deformation induced by treatment is a most important end-point and a requirement in the preclinical development programme (see section 4.8).

The choice of end-point to be measured will depend upon the stage of drug development. For example, screening tests designed to determine the anti-