

WHO COLLABORATING CENTRE  
FOR METABOLIC BONE DISEASES

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Proposal for renewal of designation as a  
WHO Collaborating Centre

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## **Introduction**

The Centre for Metabolic Bone Diseases at Sheffield has been a WHO Collaborating Centre since 1991. During that period it has collaborated with the WHO through its work programme and by WHO sponsored activities. These, detailed in part IV (Report of activities), have had a significant international impact on the field of skeletal disease, particularly in osteoporosis. Significant milestones include the WHO operational definition of osteoporosis and the WHO guidelines for preclinical evaluation and clinical trials in osteoporosis. These achievements and the work arising therefrom have resulted in the development of practice guidelines in collaboration with Governmental and non-governmental agencies.

Despite the advances in diagnostic methodology and the development of effective interventions, there are large gaps in our strategic planning to tackle osteoporosis world wide. A major problem is who to treat since current methods of identifying individuals susceptible to osteoporotic fracture lack sensitivity. Moreover, there are large regional differences in fracture risk world wide. Resolving these problems will require more detailed knowledge of the epidemiology of osteoporosis and its consequences for individuals and healthcare agencies. It will also require knowledge of how best to utilise risk factors for the identification of susceptible individuals. These issues have been discussed within the WHO, International and National Agencies and form the basis for the continuation of the Centre's collaboration with the WHO.

## PART I – DESCRIPTION OF THE CENTRE

### A. Centre Identification

#### 1. *Name and address of the Institution:*

University of Sheffield Medical, School, Beech Hill Road, Sheffield, S10 2RX, UK

Telephone number:	44 114 271 2649
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Affiliation of the Institution: University

Major source of fund support: University

Name of the Head of the Institution: Professor John A Kanis

#### 2. *Name and details of the Unit of the Institution which would act as the WHO Collaborating centre:*

Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Beech Hill Road, Sheffield S10 2RX, UK

#### 3. *Title of WHO Collaborating Centre:*

WHO Collaborating Centre for Metabolic Bone Diseases

#### 4. *Name of Director of the Institution*

Prof John A Kanis

#### 5. *Name and title and details of the proposed head of the WHO Collaborating centre:*

John A Kanis, Professor in Human Metabolism and Clinical Biochemistry / Honorary

Consultant Physician - CV attached in Appendix 1.

6. ***Statutory functions of the Institution***

The Centre for Metabolic Bone Disease is part of the Faculty of Medicine within the University of Sheffield. The Unit's activities are undertaken through its research laboratories and the clinical resources provided by the Royal Hallamshire Hospital. The major activities of the Unit are in clinical research of bone disease which is undertaken through a dedicated Metabolic Unit and out-patient clinics. The laboratory activities support this research and have their own independent basic research activities in bone disease.

Its expertise includes basic research, clinical research, epidemiology, health technology assessment and health economics.

The centre has extensive collaborative links world wide, and supports and coordinates international research with the WHO, International Osteoporosis Foundation, the European Community and research centres.

**B. Administrative structure**

1. ***Organization***

The head of the centre is Prof J A Kanis. Prof Kanis' deputy is Dr E V McCloskey, to whom the medical and key research support staff report.

2. ***Administrative and scientific responsibility***

Prof J A Kanis is responsible for the scientific work of the centre. Administration is supported by Ms W Pontefract, his secretary and personal assistant.

### 3. *International and National Advisory Boards*

The centre is involved with many agencies to formulate national and international policy and research activities in osteoporosis.

#### *International Osteoporosis Foundation*

The aims of the Foundation, founded by the Centre, are to promote international awareness and research into osteoporosis. Meetings are held at least 6 monthly.

The Centre's commitments are

- Committee of Scientific Advisors (JA Kanis)
- Board of Trustees (JA Kanis)
- Ad hoc committees on scientific projects (JA Kanis)
- Committee of National Societies (EV McCloskey)
- Scientific Committee World Congresses on Osteoporosis (JA Kanis)

#### *European Community*

The centre is on the steering committee that is investigating the incidence of vertebral fracture in Europe, supported by the EC.

Project management group (JA Kanis)

Research project (EV McCloskey)

#### *Royal College of Physicians, London*

A working group that is responsible for the development of practice guidelines for the assessment and treatment of osteoporosis in the UK.

Working group member (JA Kanis)

Consultant (EV McCloskey)

#### *Osteoporosis 2000*

A UK registered charity that aims to inform sufferers of osteoporosis and offer support services to patients and physicians. The charity was initiated by the staff of the Collaborating Centre. It holds Board meetings 3 monthly.

Chairman (EV McCloskey)

Patron (JA Kanis)

***American Society of Bone and Mineral Research***

A US based scientific society. The society holds an annual international meeting on metabolic bone disease and the unit serves on the programme committee.

Programme Committee member (JA Kanis)

***British Menopause Society***

This is a scientific society formulating policy and hosting scientific meetings on issues related to women's health and the menopause. Professor Kanis was a co-founder. The board of management meets two monthly.

Board member (JA Kanis)

***Atomic Energy Authority***

The Authority supports international scientific research. Dr EV McCloskey is the Chairman of the programme investigating international differences in peak bone mineral density.

Project Chairman (EV McCloskey)

***International Osteoporosis Foundation / WHO***

The current programme of work of the Centre includes the development of assessment guidelines for osteoporosis. The programme includes collaborations with research centres worldwide. The core group involves members of the collaborating centre and outside expertise in Epidemiology, Health Economics and Mathematics in Sweden.

There are group meets monthly with ad-hoc meeting with collaborating groups.

Programme Chairman (JA Kanis)

***Paget's Disease Foundation (USA)***

The Foundation acts as a support agency for individuals with Paget's disease and other rarer forms of bone disease. It also hosts scientific meetings. The scientific board meets yearly.

Scientific Advisory Board (JA Kanis)

***WHO***

Ad hoc advisor on osteoporosis

Chairman and member of study groups (see part IV)

***Department of Health (UK)***

The Centre coordinates a health technology programme to investigate the efficacy and health economics of the treatment of osteoporosis. The activity involves collaborating groups from the UK and meetings monthly.

Chairman (JA Kanis)

Member (EV McCloskey)

***Scientific Publications / Journals***

The centre is the European Editorial base for the Journal, Bone. The administration is undertaken by Ms W Pontefract and the European Editor is Prof JA Kanis. In addition, Prof Kanis sits on the editorial board of several journals in medicine and bone disease (see appendix 1).

***4. Existing staff***

<i>Name</i>	<i>Title</i>	<i>Area of responsibility</i>
Prof. John A. Kanis	Professor/Director	Director
Miss Wendy Pontefract	Secretary	Personal Assistant to JAK
Dr. Eugene McCloskey	Senior Clinical Research Fellow	Coordination of clinical research
Mrs. Janette Spencer	Secretary	Secretary to EMcC
Mr. Robert U. Ashford	Clinical Research Fellow	Research & service commitment
Mr. Abhijit Dey	Clinical Research Fellow	Research & service commitment
Mrs. Adrienne Richards	Hips Study Monitor	Hip fracture studies
Mrs. Anne Ball	Hips Study Co-ordinator	Hip fracture studies
Mrs. Ann Hinch	Community Research Nurse	
Mrs. Jennifer Cliffe	Community Research Nurse	
Mrs. Anne Creek	Community Research Nurse	
Mrs. Linda McGowan	Secretary (CSUH)	
Sister Veronica Edwards	Practice Nurse (CSUH)	
Miss Susanne Green	Receptionist (CSUH)	
Mrs. Betsy Kohler	Research Associate	
Mrs. Linda Longmore	Hips SAE Nurse	
Mrs. Marie Phillips	Hips SAE Nurse	
Mrs. Sharon Turton	Community Research Nurse	

The unit has the necessary manpower and laboratory and statistical services. It has a long track record of training and international collaborations.

## PART II – WORK PLAN

### **1. *Terms of reference***

1. To characterise the burden of osteoporosis world-wide.
2. To make proposals on the development of evaluation algorithms for assessment and management of osteoporosis.
3. To initiate the implementation programme of the new strategy on prevention and management of osteoporosis.
4. To develop sets of user-friendly documents for different sections of the populations.

### **2. *Relation to WHO objectives***

WHO resolution 28.82 (1975) gave support to studies on the biology, epidemiology and prevention of osteoporosis. Our activities and proposals are also in line with the conclusions of the joint WHO/EOPF/NAIMS (NIH) Consultation on Osteoporosis (NCD/OND/OSTEO/88.1) recommending increasing awareness of and research activities in osteoporosis. Many activities of the centre accord with recommendations of the WHO Study Group on the 'Assessment of fracture risk and its application to screening for postmenopausal osteoporosis' (WHO Technical Report Series 843, 1994), the Bone and Joint decade (in preparation) and the WHO Task Force on Osteoporosis (report in press).

### **3. *Reporting and time frame***

1. Burden of osteoporosis.  
Year 1. Epidemiological review complete  
Year 2. Research on utilities complete

- Year 3. Burden of disease characterised
- Year 4. Finalisation and dissemination of report
- 2. Evaluation algorithms in osteoporosis
  - Year 1. Construction of model
  - Year 2. Model synthesis
  - Year 3. Model validation
  - Year 4. Finalisation and dissemination
- 3&4. The nature of materials and targets will be dependent upon continuous consultation between WHO, the Collaborating Centre and the IOF. The resource documentation likely to be available are
  - Year 1. WHO Task Force
  - Year 2. Bone and Joint Decade
  - Year 2. Evaluation algorithms
  - Year 3. Burden of disease

Reporting will be to the Responsible Officer, Dr N Khaltaev. It is anticipated that the International Osteoporosis Foundation will support a part-time Technical Officer to establish the time frame for common goals. It is anticipated that all terms of reference would be initiated immediately. A finite time frame is expected, the 2<sup>nd</sup> Term of Reference to be complete within two years.

#### **4. *Language of correspondence***

English.

### **PART III – DESCRIPTION OF ACTIVITIES**

#### **1. To characterize the burden of osteoporosis world-wide**

A WHO scientific group on the burden of musculo-skeletal conditions at the start of the new millenium met in Geneva from the 13<sup>th</sup>-15<sup>th</sup> January 2000 in collaboration with the

Bone and Joint Decade. The meeting was opened by Dr Gro Harlem Brundtland, Director General of the WHO.

This initiative aims to identify the global burden of musculo-skeletal conditions, in order to formulate future needs and treatment strategies. The remit includes osteoporosis. The meeting identified that much of the data required to characterize burden world-wide is not really accessible. The aims of this work programme are to assemble the information required to characterize the burden of osteoporosis.

A particular problem in giving a priority for the role of osteoporosis amongst non-communicable diseases is its variable epidemiology around the world. This has been best characterised for hip fracture outcomes, but little is known concerning variations in other fractures that occur world wide. Epidemiological studies of fracture types will be undertaken and, in particular, to determine whether the pattern of fracture differs in different communities. A further unknown is the burden of osteoporosis in society. This is usually estimated from patterns of incidence, but estimates are more informative if they include the mortality and morbidity that arises. One approach, favoured by the WHO is to quantify burden of disease by life years lost due to premature deaths and life years lost due to morbidity. The latter is computed from utilities lost due to fracture. the sum of the disability adjusted life years lost (DALY's).

We have the necessary tools to investigate this thoroughly in collaboration with Dr R Lozano (WHO). The large investment by the WHO in other diseases means that a wealth of comparable data will be available to help prioritise health care priorities in different regions of the world. The characterisation of the burden of disease will need a large amount of research on epidemiology, demography and utilities in osteoporosis. These will be undertaken within the Collaborating Centre over a 1 year period. Thereafter, a collaboration is planned with Dr Rafael Lozano (WHO) in order to compute disabilities in a manner consistent with the WHO approach. The activity will be coordinated by the Director of the Collaborating Centre.

2. To make proposals on the development of evaluation algorithms for assessment and management of osteoporosis.

Current practice guidelines for the assessment of patients have several difficulties. None is suitable for international use. Those produced by non-governmental organisations are either conservative (eg guidelines of the European Foundation for Osteoporosis – now the International Osteoporosis Foundation) or border on a population screening strategy (eg physicians guidelines of the National Osteoporosis Foundation, USA). It is likely that current clinical science would permit a middle course to be struck within these extremes with high scientific rigour and validity.

The objective of this development programme is to provide international and validated practice guidelines for the identification of patients at high or low risk of osteoporotic fracture. The aim is to optimise the sensitivity (detection rate) of assessment so that therapy can be better directed. The programme does not consider specific pharmacological interventions. The approach is a case-finding strategy where risk factors are identified to quantitate absolute risks. The programme does not cover generalised population screening, but could form the basis for its subsequent consideration.

This programme of work is currently within the terms of reference of the WHO Collaborating Centre at Sheffield. The project also has the support of the International Osteoporosis Foundation who have committed funding for a meeting of their scientific advisors to review the programme. As detailed below, a large number of leading investigators are involved with the programme.

Work over the past two years has clarified many of the features necessary for improved guidelines. A central component is that the threshold for the diagnosis of osteoporosis using the WHO criteria is not appropriate as an intervention threshold. The use of the T-score alone is inappropriate since age is a greater risk factor than BMD. Rather,

intervention thresholds should be based on the assessment of risk, and in particular that risk which is amenable to an intervention. We have identified problems with the use of relative risks, and have contributed to the view, now increasingly accepted, that intervention thresholds should be determined according to absolute probability of fracture. A 10 year probability is preferred to lifetime risks because:

- a. Assumptions on future mortality introduce increasing uncertainties for risk assessment over more than 10 years.
- b. Treatments are not generally given feasibly over a lifetime.
- c. The long-term prognostic value of risk factors, in particular BMD, decreases with time.
- d. The 10 year interval accommodates clinical trial experience of interventions (generally 3-5 years) and the reversal phase (offset time) when treatment is stopped.

A model will be created that is based on the hazard functions for fractures and for death in Sweden, which is used to compute the long-term probability of different fracture types. The model will accommodate risk factors that currently include age, sex, BMD at the hip and elsewhere, other densitometric investigations (eg QUS) and clinical risk factors such as personal fracture history, family history, body mass index, smoking etc. The possible inclusion of other risk indicators is to be considered as the model develops. Examples include the biochemical indices of skeletal turnover.

The model will be initially based on the population of Sweden because of the robustness of epidemiological data. The absolute risk of fracture, however, differs markedly between nations. The pattern of osteoporotic fracture is, however, broadly similar across nations. Since extensive epidemiological data exist world wide for hip fracture, the methodology will be devised to quantify osteoporotic fractures from hip fracture rates. Osteoporotic fractures will also be weighted according to the disability sustained utilising cumulative disutilities. This technique reduces the multiple outcomes of osteoporosis to a

common currency. It also permits a health economic evaluation to justify intervention thresholds.

The model will undergo a phase of 'synthesis', where risk functions are added for risk factors. Some pilot work has been undertaken from prospective cohort studies available at Rotterdam and Gothenberg. The synthetic phase will also include data sets from cohorts in Kuopio, Sheffield, Canada (CAMOS), EVOS/EPOS (Europe) and Rochester (USA) which are at our disposal. A large number of additional cohorts may be available for assessment in collaboration with the relevant investigators. Cohorts include SOF (San Francisco), NORA (USA), Women's Health Initiative (USA), Asian Osteoporosis Study (4 Asian countries), DOES (Australia), EPIDOS (France), OFFELY and MINOS (France).

Data from cohorts available over the first year will be utilised to test the international robustness of risk factors, the inter-relationship between risk factors, and where appropriate data will be combined by meta-analysis. The next phase will utilise remaining data that becomes available for a phase of validation, though meta-analysis can still continue.

It is anticipated that the programme will be reviewed by a working group comprising a selection of the principal investigators of the major cohorts and also by the IOF. It is expected that the resource document would provide a platform for a WHO consultation or study group meeting by 2002 and user friendly guidelines developed thereafter (see Part III, 4).

### 3. Initiation of the implementation programme of the new strategy on prevention and management of osteoporosis.

The centre has played a key role in the WHO study group meeting for the platform for this initiative and will be responsible for editing the platform publication. Part of the preface statement is reproduced below.

After a landmark WHO Study Group Meeting report 'Assessment of fracture risk and its application to screening for postmenopausal osteoporosis', Geneva 1994, osteoporosis is recognised as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan, and causes more than 2.3 million fractures annually in the United States and Europe alone. The estimated life-time risk for wrist, hip and vertebral fractures has been estimated to be in the order of 40% - in other words very close to that of coronary heart disease. Osteoporosis is not only a major cause of fractures, it also ranks second among diseases that cause people to become bedridden with serious complications, even taking into account the age of patients. Because osteoporosis also causes back pain and loss of height, the prevention of disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence in the elderly population. The fifty-first World Health Assembly, May 1998, having considered the report by the Director-General on noncommunicable disease prevention and control, which described the high rates of mortality, morbidity and disability from major noncommunicable diseases - including osteoporosis - requested that the Director-General formulate a global strategy for prevention and control of noncommunicable diseases. This Scientific Group Meeting is a direct response to the WHO Resolution. It is expected that the report of this meeting will lead to the improvement of the diagnosis and care of osteoporosis patients throughout the world and make a valuable contribution to the development of a global strategy.

Further activities will provide consensus material from this document intended for specific target groups (ministries of health, health care purchasers, researchers, physicians and allied health care professionals and for patients and sufferers. It is expected that the projects would be prioritised with the Responsible Officer throughout the period of collaboration. The responsibilities, administrative structure and participation of the WHO are set out in Part III, Section 4.

4. To develop sets of user-friendly documents for different sections of the population.

The WHO strategy on prevention and management of osteoporosis provides a resource document from which materials relevant to different sectors can be drawn. As mentioned (Part III – 3) it is expected that priorities would be decided between the responsible officer and the Collaborating Centre. There will be a need to target specific segments of the community and the joint collaboration between the WHO and IOF could play a key role in dissemination of such material. It is suggested, therefore, that these developments are coordinated by a joint committee representing these interested parties.

The programme of work detailed under part III 1 and 2 will also provide resource documentation. It is intended that international guidelines for patient assessment are developed in a user-friendly way that is amenable for use by primary care physicians. Details of the approach being considered are given in appendix 2.

The WHO Collaborating Centre at Sheffield has a world wide international reputation in osteoporosis and other metabolic bone diseases. Its staff are called on regularly to teach world wide to post-graduates and other health care professionals. They also lecture at many international congresses and training courses. It is expected that these activities will continue throughout the duration of the collaboration. The unit also participates in formulating policies and position papers including:

- International Consensus Conferences
- National guideline development in the UK and abroad
- Health technology assessment
- Health economic analysis

These activities will also continue and be coordinated by either Professor Kanis or Dr McCloskey, as appropriate.

## PART IV – REVIEW OF ACTIVITIES

The centre at Sheffield has been a Collaborating Centre since 1991. Milestone achievements include:

1. The formulation of the definition of osteoporosis, now accepted world-wide (WHO Technical Report, 1994).
2. A position of the assessment of fracture risk in osteoporosis, that is widely accepted (WHO Technical Report, 1994).
3. A position on 'Guidelines for preclinical evaluation and clinical trials in osteoporosis', published by the WHO in 1998. This has helped shape regulatory strategies in Europe (CPMP), the United States (FDA) and Japan (Ministry of Health).
4. Participation in the bone and joint decade study group meeting (1999). The resource will provide a platform of continued activities, particularly in assessing the burden of disease (see Part III).
5. The WHO Task Force on the strategy for prevention and management of osteoporosis, to be published shortly (2000/2001).
6. The publication of more than 500 research papers on metabolic bone diseases, including award winning textbooks.

The following section reviews the specific activities of the Collaborating Centre over the past 4 years. Numbers in parentheses refer to the bibliography.

### **Osteoporosis**

The programme of work has reflected the enormous increase in interest in osteoporosis and recognition that this is a major contributor to morbidity from non-communicable diseases. The WHO Study Group on the assessment and diagnosis of osteoporosis (Chaired by this Centre) has set the stage for an operational definition of osteoporosis (13, 64). This has impacted world-wide. The contributions of the Collaborating Centre have

included input to the Middle East (37, 50), the Far East (87). Over the past few years it has become evident that the WHO criteria, whilst suitable for descriptive epidemiology and drug development, cannot provide intervention thresholds. Thus, the field is moving towards the distinction between diagnostic thresholds and intervention thresholds (13, 64, 127, 128).

### *Guidelines*

The WHO Study Group on assessment of fracture risk in screening for osteoporosis provided a platform for the development of practice guidelines. These have begun with initiatives by the European Foundation for Osteoporosis (now the International Osteoporosis Foundation) and the publication of its guidelines (5, 45). This European perspective has now been recognised by the European Community as well as practice guidelines in member states world-wide (12, 14, 16, 24, 118, 119). There is an important gap between the approaches used in the United States and Europe (125).

### *Hip fracture*

The Centre has undertaken studies on the epidemiology of hip fracture in part using the MEDOS study. The MEDOS study has been completed with the publication of the incidence of hip fracture in European countries and in particular the risk factors in men (99). Risk factors have been quantified with respect to falls (73, 8), lifestyle factors (10), mental function (20).

Predictions for the size of the problem of hip fracture have been researched from data on the incidence of hip fracture available in many member states. From population demography available through the World Health Organization we have made predictions for future risk of hip fracture to the year 2050 (49, 26). These projections are particularly robust since hip fracture occurs in late life in individuals who will sustain hip fracture in the year 2050 have already been born. It is likely that the age and sex specific risk will continue to increase as it has done in many member states over the past years. Hip

fracture projection that assume approximately 4 million hip fractures in 2050 may be increased several fold if the secular trend continues.

Quantitating risk of hip fracture has become an important problem and we have gradually developed the methodology for the evaluation of risk (113, 4). Apart from the risk factors such information requires detailed knowledge of the incidence of first hip fracture and how this translates into fracture probabilities (130, 124, 114, 97, 96, 80). The quantification of absolute risk and the interrelationship with risk factors will provide a platform for the development of assessment algorithms for the new terms of reference. It will be important that such algorithms lie within a favourable health economic environment, and we have established the tools to achieve this (93).

#### *Vertebral fracture*

The Centre is on the steering committee of the EVOS study which has delineated the prevalence of vertebral osteoporosis in 17,000 individuals randomly drawn from population centres in 18 member states (25). A great deal of information has now accumulated from this study on the risk factors associated with vertebral fracture. These include hormonal status (51), physical exercise (52), alcohol consumption (57). In addition, the prospective phase of the study has characterised the interrelationships between vertebral fracture risk and bone mineral density (59), stature (60), family history (67) and the relationship between vertebral fracture and aortic calcification and osteophytosis (68, 107).

There is now an emerging consensus as to how to characterise the presence or absence of vertebral fracture (126). There is, however, a great deal of uncertainty as to the morbidity which arises. This is because a proportion of individuals with vertebral deformities visible on X-ray do not present to healthcare agencies. For this reason it has been important to develop instruments to assess quality of life of affected individuals which have been developed in collaboration with the International Osteoporosis Foundation (790, 47, 106). It is clear that back pain may occur even though these patients may not

attend their physicians (111). The direct hospital costs of vertebral fracture have not been quantified. We have, however, undertaken a register study from several countries for in-patient admission for vertebral fracture. We have shown a significant relationship between the incidence of hospitalisation for vertebral fracture and discharge rates for hip fracture (41). This permits estimates of the burden of vertebral fracture to be made (41) from the incidence of hip fracture. This will be important in defining the global burden of disease. Knowledge of risk factors is also important in devising assessment algorithms and of particular importance is that the major risk indicators for hip fracture are also shared by vertebral fracture (133).

#### *Treatment of osteoporosis*

The Centre has been involved in formulating treatment strategies in osteoporosis with a number of healthcare agencies (121, 120, 76, 91, 44, 103, 39). In addition, a variety of studies have characterised the importance of therapeutic intervention, particularly with respect to hormone replacement therapy (30, 35, 36, 74, 21), the bisphosphonates (19, 53), the calcitonins (90, 108), raloxifene (95), progestogens (9) and nutritional status for calcium (82, 85, 102), and vitamin D (62, 63, 43, 116). In assessing the impact of interventions on therapeutic strategies is important to take account of the offset of effect once treatment is stopped since many treatments are not given over a lifetime. We have drawn attention to this problem (98, 107, 123) and these have been incorporated into guidelines for drug development in collaboration with the WHO (78). The Centre has been involved in guideline development for regulatory agencies including the WHO, the FDA and the EMEA (78, 89, 23).

#### *Assessment and diagnostic techniques*

There has been a great proliferation in the availability of diagnostic techniques and the Centre has participated in their evaluation for ultrasound (18, 58, 34), bone mineral density by dual energy X-ray absorptiometry (75, 69, 38, 104), biochemical markers of bone turnover (55), as well as histological techniques (15). Such studies will provide a platform for the interaction of risk factors and technology in accurate fracture prediction

(92), which provides a platform for the terms of reference for this programme (part III – 2).

#### *General education*

The Centre has participated actively in the dissemination of information in the form of Textbooks (27, 32), slide atlas (28), as well as general reviews on the burden of osteoporosis, future predictions and global strategies (46, 70, 71, 81, 86, 110, 112, 122, 115, 117).

#### **Neoplastic bone disease**

We have completed a research initiative in breast cancer to characterise the effects of skeletal agents on the natural history of skeletal metastases. We have completed studies of the effects of tamoxifen on breast cancer (1) and shown an adverse skeletal effect in premenopausal women. A major programme has been to evaluate the effects of bisphosphonates on metastatic disease (22, 65, 31, 61, 33). In women with breast cancer relapse but without evidence of skeletal metastases we have shown a highly significant effect of a bisphosphonate to decrease the burden of skeletal metastases (22). This is associated with a preservation of bone mass (77), and it seems probable that the decrease in bone resorption and decrease in skeletal morbidity may be related to the induction of skeletal metastases (100). Studies are continuing with clodronate (65) as well as some of the newer bisphosphonates (109).

We have undertaken a large number of studies to characterise the natural history of skeletal disease due to myeloma (40) with a particular emphasis on the ability of bisphosphonates to alter the expression of this disorder on the skeleton (56, 72, 132).

#### **Paget's disease**

We have continued to develop therapeutic strategies aimed at the long-term control of disease activity (2, 3, 42, 129).

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**Education and qualifications**

Surbiton County Grammar School

University of Edinburgh 1964-1970

BSc (Hons) 1st Class	University of Edinburgh, 1967
MB ChB	University of Edinburgh, 1970
MRCP (UK)	Royal College of Physicians, Edinburgh, 1972
MA status	University of Oxford, 1977
MRCPath	Royal College of Pathologists, 1982
FRCP (London)	Royal College of Physicians, 1984
MD	University of Sheffield, 1985
FRCP (Edinburgh)	Royal College of Physicians, 1986
FRCPPath	Royal College of Pathologists, 1992

**Present appointments**

Professor in Human Metabolism, University of Sheffield, from 1991.

Consultant Physician, Sheffield Area Health Authority, from 1979.

Physician in administrative charge of Metabolic Unit, Royal Hallamshire Hospital, from 1979.

Director, World Health Organisation Collaborating Centre for Metabolic Bone Diseases, from 1991.

**Honorary appointments**

Scientific Advisory Board, Paget's Disease Foundation (USA), from 1986.

WHO Advisor on Osteoporosis from 1988.

Founder and Trustee, European Foundation for Osteoporosis and Bone disease (now the International Osteoporosis Foundation), from 1987.

Council and Founder Member: British Menopause Society, from 1989

Board Member, Health Council on Osteoporosis, from 1992

Board Member, International Bone and Mineral Society

**Current Editorial appointments**

Editor	Bone	1990-
Editorial Board	Journal of Bone and Mineral Research	1991-
Advisory Board	Hormones & Metabolism	1987-
Advisory Board	Revista Espanola de Enfermeda Des Metabolicas Ossias	1991-
Editorial Board	Italian Journal of Mineral & Electrolyte Metabolism	1990-
Editorial Board	Osteoporosis International	1990-
Editorial Board	Trends in Endocrinology & Metabolism	1989-
Editorial Board	Quarterly Journal of Medicine	1990-

**Previous appointments**

Medical Research Council Clinical Research Fellow, Renal Unit, Churchill Hospital and Metabolic Unit, Nuffield Orthopaedic Centre. October 1974 to July 1976.

Wellcome Senior Research Fellow in Clinical Science and Lecturer in Medicine, Nuffield Department of Medicine, University of Oxford. August 1976 to September 1979.

Senior Lecturer and later Reader in Human Metabolism, Department of Human Metabolism and Clinical Biochemistry, University of Sheffield, October 1979 to October 1991.

**Research interests**

Largely related to disorders of skeletal metabolism including osteoporosis, Paget's disease of bone, hyperparathyroidism, renal osteodystrophy and neoplasia affecting the skeleton. Contributions to research include cell biology, histomorphometry of bone, assessment and treatment of bone disorders, guideline development, health technology assessment, epidemiology and health economics. Author of more than 500 papers, chapters and books on bone disease and metabolism since 1976.

**Books published**

Kanis, JA (1991) Pathophysiology and treatment of Paget's disease of bone. Martin Dunitz: London.

Kanis, JA (1994) Osteoporosis. Blackwell Science, Oxford.\*

Kanis, JA (1996) Textbook of Osteoporosis. Blackwell Science, Oxford.

*\*awarded the Royal Society of Medicine 'best textbook' of 1995.*

**Appendix 2.**

DEVELOPMENT OF PRACTICE GUIDELINES

DISCUSSION DOCUMENT

The following considerations have to be taken into account in developing the proposed guidelines.

### **General**

1. It is intended that the guidelines would be utilised by primary care physicians and should, therefore, be easily applied in general practice without recourse to specialised knowledge of the field.
2. General practitioners are unlikely to utilise relative risks but would prefer absolute risks (fracture probability) provided that guidance is given concerning the threshold of risk at which further investigation or intervention is indicated.
3. Guidelines should accommodate men as well as women.

### **Risk factors**

1. There are a large number of risk factors that are consistently associated with fracture risk.

2. It will be important to utilise as many risk factors as possible in order to maximise sensitivity and specificity of the decision tree.
3. Some of these risk factors are more or less independent in that they predict fractures significantly when the one is adjusted for the other.

For example, a maternal family history of hip fracture increases the risk of hip fracture two-fold (Cummings et al, 1995). The relative risk falls only to 1.9 when adjusted for BMD. Thus, the risk factor can be utilised to enhance risk assessment with and without BMD.

4. Some risk factors are dependent, for example body mass index and BMD. Thus, BMI or BMD can be utilised, but their use may be mutually exclusive.
5. A third category of risk factors are partially dependent. An example is smoking and BMD. In elderly women in the SOF study hip fracture risk is increased by 1.9 but RR falls to 1.3 when adjusted by BMD. The combined risk is therefore not much greater than the risk associated with either factor alone.
6. Thus, risk factors other than age or BMD can be used to identify patients in whom densitometry is indicated (see 5) or to enhance the value of BMD (see 3 above).

7. Different risk factors have different relevance at different ages. For example, an early menopause is a significant risk factor for any osteoporotic fracture in perimenopausal women, but is of uncertain significance for fracture in the elderly. Conversely, a family history of hip fracture, is a risk factor in the elderly, but is not a consistent risk factor at menopause.
8. Different risk factors have different relevance for different fracture sites. These may in part be due to the different pattern of fracture with age (eg hip fractures are common in the elderly), but in other cases are not. An example is provided by ankle fractures where high BMI and smoking are risk factors compared to forearm fractures at the same age where these factors do not contribute significantly to risk. For forearm fractures low BMI and early menopause are important factors.
9. It is thus evident that guidelines based on risk factor assessment need to take account of age and the pattern of fracture type that varies with age. In addition, age itself is a dominant risk factor so that risk needs to be categorised by age since, if not, age dominates all assessments.
10. Clinical risk factors need to be chosen with care. They should be
  - a. Validated in multiple populations.
  - b. Adjusted for age, sex and type of fracture.
  - c. Readily assessed by primary care practitioners.
  - d. Contribute to a risk that is amenable to therapeutic manipulation.

- e. Be intuitive rather than counterintuitive to medical care. An example of the latter is dementia which carries a very high risk of hip fracture in men and women. General practitioners might, however, be reluctant to target osteoporosis treatments on the diagnosis of dementia.
11. Guidelines should accommodate measurements by peripheral devices including ultrasound technologies since they are reimbursed in many countries such as the USA. Similarly, they should incorporate other laboratory-derived risk factors such as biochemical tests and other bone mineral measurements where these are known to contribute significantly to fracture risk.

### **Fracture risk**

1. Risk based solely on hip fracture hazard underestimates the burden of osteoporotic fractures, particularly in the young. It is important that risk incorporates osteoporotic fracture burden at all ages.
2. Not all fractures are due to osteoporosis in individuals over the age of 50 years. Examples include fractures of the face and skull. A caveat is that treatments may not affect the risk of this type of fracture. An example is provided in the FIT study where treatment with alendronate had less efficacy on appendicular fractures in women without osteoporosis. A more recent example is the lack of effect of

risedronate in elderly women selected by their risk of falling compared to those selected on the basis of BMD. In determining risk thresholds account needs to be taken of these fractures that are due to osteoporosis.

3. An approach is to characterise fractures due to osteoporosis as those (a) associated with low BMD and (b) where the incidence increases with age. An alternative is to give tariff values to different fracture sites. The former approach rests on less assumptions.
4. Account needs to be taken of the morbidity of different osteoporotic fractures in setting assessment or intervention thresholds. The morbidity from hip fracture is much greater than that from forearm fractures. The approach that we have used is to weight probabilities of fracture by the disutility associated with each site of fracture, but other approaches are possible.
5. In many regions of the world, the pattern of osteoporotic fracture is unknown. In those countries where data are available (Sweden, UK, USA) the pattern is similar when evaluated by age and sex. Assuming that this holds for other countries, an index of fracture morbidity can be obtained from hip fracture risk since this risk is well documented internationally.
6. Relative risks are not appropriate for assessment guidelines since they are not widely understood. For example, relative risk associated with osteoporosis

decrease with age. In this context absolute risks are desirable. Lifetime risks are not appropriate since treatments are not generally given for life and lifetime risks do not change markedly with age. Ten year risks cover current durations of treatment and permit the inclusion of persisting effects once treatment is stopped in health economic evaluation.

### **Risk assessment**

1. Risk assessment is based on an estimate of fracture probability derived from a panel of risk factors, the weight of each being categorised by age (ie age and fracture pattern), strength of predictive value and independence.
2. The scoring system is based on the combined relative risks adjusted to the population by age. For example, a Z-score of  $-1$  for BMD at the hip has an relative risk for hip fracture of 2.6 compared to individuals with an average BMD for age but a relative risk of 1.7 compared to the population. Similarly, a dichotomous risk factor should be adjusted to the population risk according to its prevalence at each age band.
3. Independent risks can be multiplied. Totally dependent risks are mutually exclusive.

4. The combined risks are utilised to allow clinical decision making. The three decisions are:
  - a. No further assessment or treatment required.
  - b. Further assessment, eg diagnostic assessment is indicated.
  - c. Treatment indicated irrespective of any diagnostic assessment.
  
5. DXA at the hip is considered to be the diagnostic test for osteoporosis. However, the threshold of BMD for intervention will vary according to the risk factor profile including the risk contributed by age. In this sense it is utilised as a risk assessment, since in some instances intervention thresholds will be less stringent than the diagnostic threshold.
  
6. Combined risks are translated to fracture probability weighted by disutility, since the significance of fracture varies by fracture type and therefore by age.
  
7. Absolute risk is determined as a 10-year probability (see previously).
  
8. Risks weighted by utilities are categorised as low, moderate and high risk to permit decisions (as given in para 4).
  
9. It is recognised that thresholds of risk are arbitrary, but should be realistic in terms of health economic considerations.

### Other considerations

1. Health economic justification of thresholds will vary according to costs of intervention and efficacy. There are obvious arguments for not providing thresholds for each treatment available in each country at each cost. The approach suggested is to determine cost utility with a basket of treatments of average cost and effectiveness. A further reason is that practitioners decide who to treat and thereafter continue the method of treatment.
2. It is likely that effectiveness of different interventions differ. There is, however, an inadequate evidence base to provide a hierarchy of treatment based on effectiveness. It is considered, therefore, that guidelines should focus on common intervention and assessment thresholds irrespective of the intervention intended.
3. It is recognised that age - adjusted hip fracture risks and probably other fracture risks vary markedly from country to country. For example, hip fracture rates in women are 10-fold higher in rural Turkey than in France. Thus, the combined score from risk factors at which assessment or intervention thresholds are set will need to be country specific.
4. The proposed guidelines do not accommodate agents that have significant extraskeletal benefits and risks such as HRT or the SERMS. The argument for not providing different thresholds is that they evolve guidelines towards product

specificity. The argument for their provision is that cost-effectiveness is critically dependent on these extraskeletal risks and benefits. For example, a significant reduction of breast cancer risk with treatment in women with osteoporosis would mean that it would be cost-effective to treat women with a lower (less stringent) treatment threshold than with a treatment without this effect.

5. There are several front-end approaches possible.
  - (a) Pursue a policy of generic rather than product-specific guidelines.
  - (b) Provide information on extraskeletal risks and benefits within the guidelines available for general practitioners.
  - (c) Weight risk factor scores according to cardiovascular and breast cancer risk.
  - (d) Provide different assessment and intervention thresholds within the document.

Option (a) or (b) may be preferred as the front-end approach. It may be appropriate to model the effect of SERM-like and HRT-like intervention on assessment thresholds within the resource documentation.

### **Practice guidelines**

1. Attached is a provisional approach that might be adopted. Assessment sheets are provided for men and women. It is not yet clear whether separate sheets would be required. The assessment sheets list risk factors to be sought.

2. They are examples only at this stage. The several boxes next to the risk factors are age specific. A box is circled if the risk factor is present according to age. The risk factor is significant if the box contains an asterisk. This provides a mechanism whereby risk factors can be weighted or ignored depending on age or sex.
3. Three groups of risk factors are included. Two are based on clinical risk factors. They are separated to take account of the reality that some are weak (and contribute less to a total score), and some may be interdependent. The third category uses laboratory tests which are not diagnostic but contribute to fracture risk.
4. The score is computed from the number of asterisks identified. The weighting given is arbitrary, but will be based on adjusted relative risks.
5. The last sheet gives a table for men and women to compute probability of fracture according to the risk factor score. These are examples only but will be populated by 10-year risks adjusted for morbidity. Patients would be categorised as low, moderate or high risk.
6. The low risk category is likely to comprise individuals where the 10 year weighted fracture probability is 5% or less. In such individuals knowledge of BMD at the hip is unlikely to yield a probability of greater than 10%.

7. An intermediate weighted probability (5-10%) provides an indication of BMD assessment (preferably at the hip). Where further assessment is by a peripheral device the risk score would be adjusted. Where DXA at the hip is undertaken patients are categorised according to weighted fracture probability (>10%, <10%). Those in the higher risk category are recommended intervention: those in the lower risk might be reassessed after 5 years.
  
8. Those in whom risk factor analysis (without DXA at the hip) yields a weighted fracture probability might be recommended an intervention without information on hip BMD.