Effective HEALTH CARE

Screening for Osteoporosis to Prevent Fractures

Should population based bone screening programmes aimed at the prevention of fractures in elderly women be established?

Fractures of the hip, wrist, and spine in elderly women are a major public health problem. They are mainly caused by a combination of loss of bone mass (osteoporosis) and increased risk of falling which occur with ageing.

There is increasing pressure to establish combined bone screening/hormone replacement therapy (HRT) programmes in order to reduce the number of fractures in elderly women. The aim of bone screening is to identify women at highest risk of fracture. The use of HRT in these women reduces bone loss and is thus aimed at preventing fractures.

There have been no scientific trials assessing the effectiveness of population bone screening programmes in preventing fractures in elderly women.

The long term effectiveness of HRT in preventing fractures in elderly women is not known.

Bone density measurements are poor at identifying which women will go on to have a fracture in later life.

The uptake of screening and the long term compliance with HRT are low. Less than a quarter of women are likely to both attend for screening and take HRT over a long period of time.

It is likely that a bone screening programme will lead to the prevention of no more than 5% of fractures in elderly women.

Given current evidence, it would be inadvisable to establish a routine population-based bone screening programme for menopausal women with the aim of preventing fractures.

A. BACKGROUND

A.1 Fracture of the hip, wrist, and spinal vertebrae is common in the elderly especially among women. The incidence of fractures increases with age [1,2] (Figure 1). The mean age of fracture is around 75 years. The incidence of hip and spine fractures has been increasing.[3] This, combined with the increase in the number of elderly people, constitutes a major public health problem which results in a large amount of morbidity, associated mortality, and human suffering. It also represents a major claim on future health service resources.

A.2 Many of these fractures are the result of loss of bone mass, a condition known as osteoporosis. This loss results in the development of weaker bones with lower than normal density which are more likely to fracture. After reaching a peak before the age of 40 years bone density decreases with age, but this effect is particularly marked in women after the menopause, associated with declining levels of oestrogen.
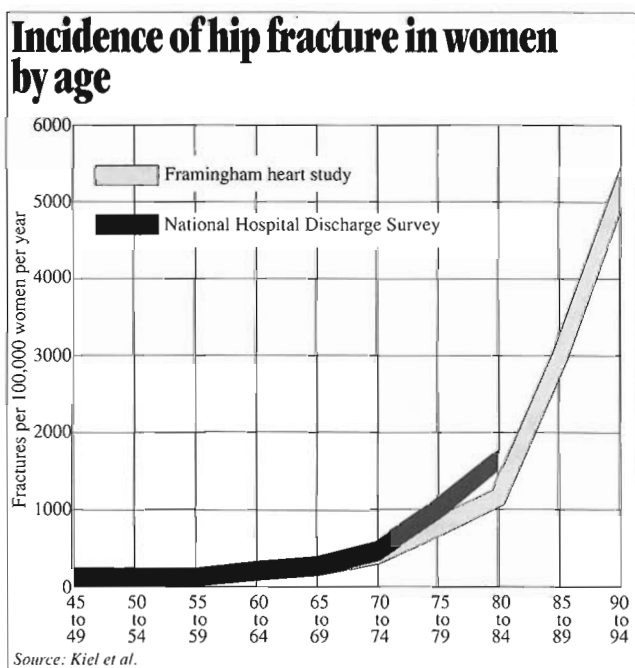
Incidence of hip fracture in women by age

Figure 1 *Incidence of hip fracture in women by age*

A.3 There is considerable pressure to set up population bone screening programmes in order to reduce the number of fractures in elderly women as part of public health policy. Bone screening is already being offered in private clinics and some health authorities. GPs are also under pressure to refer women to bone screening and HRT programmes. It is important to have conclusive evidence that screening can prevent fractures in a significant proportion of those screened, based on clear and scientifically valid criteria, before it becomes routinely available.[4] To invite women to attend for screening without such evidence of benefit raises ethical issues. Experience shows that once a health programme becomes widely used it is difficult to withdraw if it is subsequently shown to be ineffective.

A.4 Clearly a woman with specific high risk factors for a fracture in later life (eg bilateral oophorectomy at an early age) may decide to have screening and/or treatment after discussion with her doctor of all the possible risks and benefits. This decision is independent of whatever public health policy is adopted to reduce fractures in the elderly population in general.

B. TWO APPROACHES TO PREVENTION

B.1 There are two approaches to the reduction of fractures in the population.

(a) One approach is to identify a group of people at high risk of fracture by means of screening the whole population of women at the time of the menopause and then to treat this group. This is called the high risk approach.

(b) An alternative, the population approach, is to attempt to reduce everyone's risk of fracture in later life by reducing risk factors for fractures in the whole population.

B.2 This bulletin thoroughly evaluates the high risk screening approach although it returns to the population approach at the end.

C. GUIDELINES FOR EVALUATING A SCREENING PROGRAMME

A widely accepted five point guide will be used to evaluate the evidence for the effectiveness of bone screening in preventing fractures in elderly women.[5]

1. Has the programme's effectiveness been demonstrated in a randomized controlled trial (RCT)?
If a trial has not been carried out all of the following points must be satisfied:
2. Does the current burden of suffering warrant screening?
3. Are there efficacious treatments or preventive measures available?

4. Is there a good screening test?
5. Will people at risk of the disease attend for screening and will people with a positive test result comply with subsequent advice and interventions?

Each of these points is considered in turn below.

1. Has the programme's effectiveness in reducing fractures been demonstrated in a randomized controlled trial?

There have been no scientific trials assessing the effectiveness of population bone screening programmes in preventing fractures in elderly women.

1.1 The only sure way to determine the likely outcome of a screening programme is by means of a properly designed and executed randomized controlled trial.[6]

1.2 There have been no randomized controlled trials assessing the effectiveness of bone screening programmes for the prevention of fractures in later life. Since most fractures occur after the age of 75 and given the practical difficulties of running a trial over a long period of time there are good reasons to suppose that such a trial is unlikely to be funded. We therefore have to rely upon answering the points in 2-5 above to reach some conclusions on the expected effectiveness of such a programme.

2. Does the current burden of suffering warrant screening?

Fractures of the hip, wrist, and spine in elderly women are a major public health problem resulting in huge private and social costs.

2.1 Fractures in post-menopausal women are an important cause of morbidity, mortality, private and social cost.[7]

– During any five year period, 10% of a population of 70 year old women and over will suffer a hip fracture of whom 10-20% will die as a result.
– The average length of hospital stay for hip fracture is about 23 days.[8]
– Patients with hip fracture account for over 20% of all orthopaedic beds.
– The average cost per case of hospitalisation is around £2500.[8]
– After six months only about one third of survivors are fully mobile.[9]

3. Is there an efficacious treatment for the prevention of fractures?

The long term effectiveness of hormone replacement therapy in preventing fractures in elderly women is not known.

3.1 Established osteoporosis is more difficult to treat and so it is advisable to start therapy at the time of menopause before rapid bone loss occurs. HRT based on oestrogen alone or combined with progesterone has been shown to retard, stop or even temporarily reverse the process of bone loss which immediately follows menopause.[10-15]

3.2 HRT is recommended conventionally only for a maximum of 10 years, and so there will be a gap of about 15 years between stopping HRT and the time when women commonly suffer from fractures. Studies comparing those who have taken and not taken HRT show a reduction in fracture incidence of about 50%.[16-23] Most of these studies examined only a relatively young group of post-menopausal women for only a few years after starting HRT. As such they are likely to overestimate the overall protective effect of HRT in preventing fractures in elderly women. Furthermore, what is not clear is how much of the protective effect of HRT persists after the termination of treatment (Figure 2).

3.3 If the protective effect lasts for the remainder of a woman's life (Figure 2, line 2) then a significant delay in fractures will occur compared to an untreated woman (Figure 2, line 1). However there is evidence that the protective effect diminishes after treatment is stopped.[16,19,21] This is because the rate of bone loss after withdrawal of treatment may be as rapid or possibly even steeper than in untreated women at the time of menopause (Figure 2, line 3).[13,24,25] Within a few years the protective effect may have worn off. To be
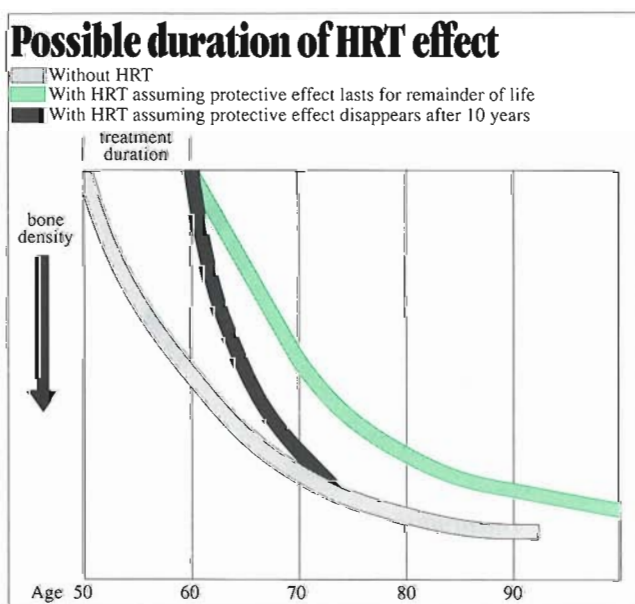
Figure 2 *Diagrammatic representation of possible duration of effect of HRT*

assured of the long term effectiveness in reducing fracture risk, treatment would perhaps have to be carried on for life.[12] There is debate over this matter[26] since the studies showing such accelerated bone loss occurred after the removal of ovaries and not natural menopause.[24]

3.4 Prospective studies have not followed women for long enough to provide reliable estimates of the long term efficacy of HRT in preventing fractures in elderly women. Until good evidence on the long term efficacy of HRT in reducing fractures, several years after stopping therapy, is obtained it is impossible to make an estimate of the net impact of a screening and treatment programme.[27]

3.5 Another source of uncertainty is whether the effectiveness of HRT estimated in these studies is the same for women with different bone densities. Most studies assume that the efficacy of HRT is independent of the initial bone mass.[28] However it is possible that HRT has a greater impact on those with less loss of bone mineral. This would also lead to an overestimate of the impact of a programme based on treating women of high risk.

3.6 In summary the effectiveness of HRT in preventing fractures much later in life when taken for ten years after the menopause by women with low bone density is not proven.

4. Is the bone density measurement a good screening test?

Bone density measurements are poor at identifying which women will go on to have a fracture in later life.

4.1 There are a variety of non-invasive techniques of measuring bone density. The DEXA method is the most precise and is most commonly used[29] and ultrasound is becoming popular.[30] (see appendix III).

4.2 A good screening test should be able accurately to distinguish between those who will not go on to have a fracture in later life (specificity) and those who will if not treated (sensitivity). If both specificity and sensitivity are both high then the test will have a high predictive accuracy in common conditions like fracture.

4.3 Women with lower bone density have weaker bones and thus are at greater risk of fracture. Follow-up studies estimate that the risk of fracture (taking age into account) increases between about 30%-70% as bone density falls by one standard deviation.[31-36]

4.4 Although women with hip fractures have an average bone mineral density which is lower than those who do not, this difference is small and there is considerable overlap[37-39] (Figure 3a). For the test to be highly sensitive and specific the separation between high and low risk women needs to be greater as in Figure 3b.

4.5 There is no accepted cut-off point for bone density below which a woman is identified as being at high risk of fracture. *With the cut-off point being taken as the lowest 20% of all bone density measurements, then only 28% of those so identified as 'high risk' would have gone on to suffer a fracture in later life in the absence of therapy.[40] More importantly, 63% of all fractures will occur in women with bone densities above this arbitrary cut-off and so will not be identified.* (see appendix I). This limits the potential effectiveness of any bone screening programme.

4.6 An alternative way of screening women would be to measure the rate of bone loss by regular screens or biochemical assessment to identify a subgroup of 'rapid bone losers'. However there are few studies to show the predictive value of this.[41] Given that the margin of error in measuring bone mass by DEXA is of the same order of magnitude as the annual rate of bone loss[42] reasonably

Distribution of bone density in women with and without hip fracture
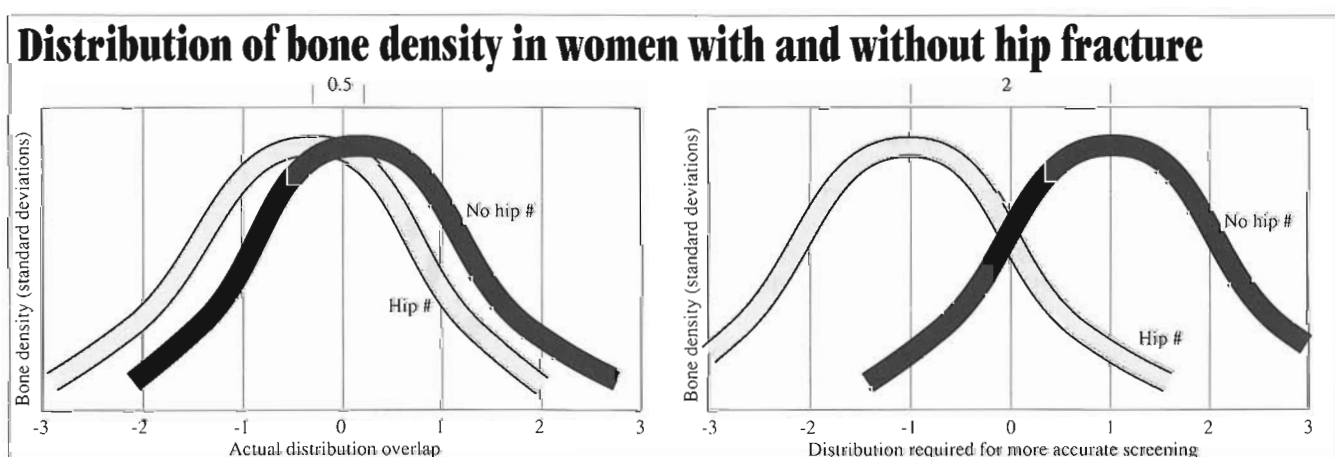
Figure 3 *Illustrative diagram of bone mass distribution of women who go on to have fracture and those who don't.*
(a) Bone density distributions with considerable overlap so poor at discriminating
(b) Bone density distributions with little overlap so good at discriminating

— *women who go on to have fracture*
■ *women who do not go on to have fracture*

4

precise estimates of the rate of loss for the whole population would require extending the length of follow-up to around four years. A recent paper has indicated that baseline bone mass combined with biochemical assessment is better than bone mass alone.[43]

4.7 Because prospective studies have so far followed up women for only a few years it is not possible to assess the accuracy of bone density measurements at the menopause in predicting those women who will go on to have a fracture in over 25 years time, when they are most common.

4.8 The predictive accuracy of bone density measurements is likely to be less than shown in these studies because other factors unrelated to bone density, such as age, are of increasing importance in determining the risk of fracture as women get older.[33] Most women's bone mass will eventually fall quite low. The majority of fractures are thought to occur as a result of the impact from a fall. Thus it is the risk of falling (affected by factors such as poor eyesight, cognitive impairment, medication, and high mobility) and other non-bone mass factors which will also be important in determining whether an elderly woman suffers a fracture.[35,44,45] So while there is little doubt that bone mass is an important factor in fracture, the question of how useful it is for predicting fractures in elderly populations, where many have a low bone mass, remains unanswered.

5. Will people at risk attend for screening and will women with a positive test result accept long term HRT?

The uptake of screening and long term compliance with HRT is low. Less than a quarter of women are likely to both attend for screening and take HRT over a long period of time.

5.1 The potential effectiveness of any screening programme will depend on the percentage of women who attend for screening (uptake) and comply with recommended therapy. Using results from the national breast cancer screening programme which targets a similar age group of asymptomatic women there is good reason to assume that even with a lot of effort uptake rate will not exceed 72%.[46]

5.2 Surveys in this country[47] and elsewhere[48] indicate that long term compliance with HRT is low at around 30%. The major determinant of women's decisions about HRT has been shown to be their current level of comfort; thus it is unlikely that many women without symptoms will take therapy for ten or more years.[49] Calculations of the net impact of the programme reported in the literature which have assumed 100% compliance[38,50-52] are therefore likely to be considerable overestimates.[27]

D. WHAT IS THE LIKELY OVERALL IMPACT OF BONE SCREENING?

It is likely that a screening programme will prevent no more than 5% of fractures in elderly women.

D.1 Several models have been used to estimate the effect of such a programme, by comparing groups of women with and without screening. Their results are strongly influenced by the assumptions made. A recent British study[40] modelled the impact of such a screening programme using assumptions which, given the literature, appear quite realistic (a screening uptake rate of 70%, sensitivity of 37%, a ten year duration of HRT, compliance of 30%). If it is assumed that HRT reduces the risk of fracture by 50% and that this protective effect lasts the rest of a woman's life then the model predicts that no more than 4% of expected hip fractures will be prevented in any one year. It also found that the costs of the screening and HRT would not be offset by the savings from the reduced incidence of fractures. Alternatively, assuming that the protective effect of HRT will have disappeared by the age of 75 years then the impact will be a reduction in fracture incidence of 2.6%.[40] This constitutes an approximate reduction of about 6 out of 219 fractures in each year in a district with population of a quarter of a million.

D.2 This study has a lower estimate of likely impact than several published studies from the USA which conclude that bone screening and associated HRT may be a cost-effective use of resources.[38,50,51] However, these results are due to estimates of the effectiveness of HRT in reducing fractures, the duration of the effect and the accuracy of the screening tests which are not justified by the literature. Even with these favourable assumptions it is accepted that screening is not cost-effective with compliance levels below 30%.[50]

D.3 Screening and HRT will affect the quality of a woman's life as well as her fracture risk and life expectancy. Some cost-utility calculations using quality adjusted life years have been published.[50-52] However they assigned utilities to health states in an arbitrary fashion. Such calculations are subject to even more uncertainty than simple effectiveness analysis described above and it is doubtful that they will be useful to decision makers in the near future.

D.4 This assessment of the evidence for population bone screening is supported by several other independent reviews.[4,37,50,53] In addition the US Preventive Services Task Force recommended against routine screening to detect osteoporosis,[54] as did the Canadian Task Force on Periodical Health Examinations.[55] There have also been calls for a randomized controlled trial to be established to assess the impact of HRT on fractures.[56] However other reports have recommended screening around the menopause.[57]

E. WHAT ARE THE COSTS ASSOCIATED WITH SUCH A PROGRAMME?

E.1   A population screening programme requires considerable commitment and use of local resources. It would involve the establishment of population registers, recall mechanisms, GP referral and treatment channels, counselling and follow up facilities. This would all have to be based on cost-effective guidelines that identify an optimal bone mass threshold for the institution of HRT. These are not yet available due to the uncertainties discussed above.[46] Given the problems experienced in the breast cancer and cervical cancer screening programmes, health authorities would have to consider these logistical and management factors very carefully before funding a programme even if there were conclusive evidence of the potential effectiveness of such a programme.

E.2   There are significant psychological costs associated with screening people with no symptoms some of whom are then labelled as 'high risk' for a disease. Given the time lag of around 30 years between screening and the age when fractures are most common, along with the length of time women are recommended to take HRT, this could significantly increase anxiety. This is particularly important for those women who are wrongly labelled as high risk due to the poor predictive accuracy of the screening test.

E.3   The capital cost of a DEXA machine is about £50 000 with a useful life of around seven years. The costs of accommodation are around £15 000-35 000 per year and the estimated running costs (including two operators, maintenance and administration) are about £45 000-50 000 each year. Additional to this is the maintenance of a register and the call and recall mechanisms. The cost of HRT prescription is around £50.00 a year per woman. Two GP check ups per year will also be needed for women on therapy (about £5.00 each). There are also the private costs to women of travelling and time. The major cost element in the programme is thus the therapy and follow up, not the initial screening.

E.4   A study in an English region of 4.6 million people with around 27 000 post-menopausal women aged 50 each year (1.14% of females of all ages) estimated that the annual cost of such a programme would be about £75 000 for screening and about £770 000 for HRT and follow up once the programme had been running for ten years and was in a steady state.[40]

F. WHAT ARE THE ALTERNATIVES?

F.1   Given that a screening approach is unlikely to have a significant impact on reducing fractures in elderly women other strategies are worth investigating. Work is in progress examining alternative and possibly more accurate methods of identifying women at risk when they are already elderly, taking into account a range of contributory factors such as neuromuscular function, strength, or dementia.[58] There are also some common-sense interventions that health authorities could consider in aiming to reduce the risk of fractures in the elderly. These include:

– encouraging scrupulous management of drug therapy for other conditions;
– minimisation of external hazards in the immediate environment such as the home and street.

F.2   This bulletin thoroughly reviewed only the evidence for population osteoporosis screening. However there is a considerable literature examining the alternative approach to prevention mentioned in section B above. This concentrates on reducing risk factors of fracture in the whole population. The literature indicates that it would be worthwhile for health authorities to investigate the use of population preventive programmes. These could include stopping smoking, exercise, and adequate calcium intake in childrens' diets.[37]

CONCLUSION

Given current information, it would be inadvisable to establish a routine population-based bone screening programme for menopausal women with the aim of preventing fractures.

EFFECTIVE HEALTH CARE: REVIEWING THE EVIDENCE

Effective Health Care is produced using a step by step process. The objective is to provide valid and systematic data to aid managers and clinicians in purchasing and providing health care services. Three principal criteria are employed: clinical effectiveness, cost effectiveness, and acceptability.

The process of review and synthesis of the evidence for each target health care intervention is divided into a number of stages (Figure 1). It is modelled on established methodological checklists used within the Canadian Task Force on the Periodic Health Examination and as illuminated by Woolf *et al.*, and the U.S. Preventive Services Task Force.[1-3]

Figure 1: *Overview of the Review Process*

WHAT QUESTIONS SHOULD THE LITERATURE BE ANSWERING?
- identify key studies and clinical experts
- clarify causal pathways

HOW WELL DO DIFFERENT TYPES OF STUDY ANSWER THESE QUESTIONS?
- hierarchy of evidence (study types)

HOW VALID IS THE INFORMATION GIVEN BY EACH STUDY?
- internal validity
- external validity
- statistical power

LOOKING ACROSS THE STUDIES, WHAT DOES THE EVIDENCE SHOW?
- quantitative meta-analysis of clinical effectiveness
- cost effectiveness evaluation
- acceptability issues

WHAT IS THE OVERALL IMPACT OF THE INTERVENTION?
- balance of risks and benefits
- health service context
- inter-sectoral implications
- target groups
- public health impact

Step 1: Clarifying the question:

Once a topic area for a bulletin has been identified (for example, osteoporosis) and the purchasing question specified (should population bone screening and treatment programmes for the prevention of fractures in post-menopausal women be established?), the next task is to clarify the areas and issues that need to be addressed through the available literature. This is done in three ways.

i An initial search of the literature is conducted to access important studies in order to define the cogent issues which will be addressed in the bulletin.

ii Clinical experts in the particular field of study are identified with the help of the Royal College of Physicians to assist in searching the literature and establishing the questions to be addressed.

iii The analytical tool of causal pathways is used to highlight the type of evidence that must be examined in order to evaluate the intervention.[2,4]

Figure 2 illustrates the causal pathways for osteoporosis. The most direct evidence of the effectiveness of bone mass screening would come from link 5, in studies demonstrating that a population of asymptomatic women for whom bone mass is measured and treated with HRT will have a reduced incidence of fracture. A randomized

Figure 2: *Causal Pathways For Osteoporosis*
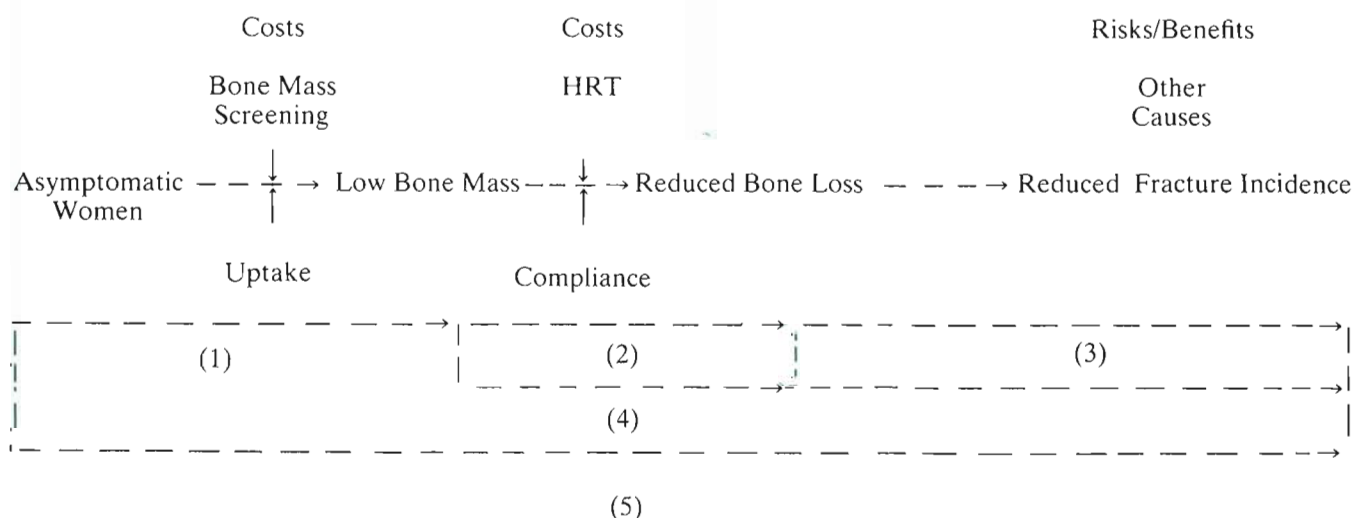
controlled trial would provide the strongest evidence for this link (though it may well not be feasible). In the absence of such evidence, it may be possible to infer effectiveness by combining links 1 and 4, or links 1, 2 and 3, and examining the evidence for each of these links separately.

Step 2: Establishing a hierarchy of studies and of evidence:

Within clinical epidemiology a hierarchy of types of studies can be delineated. It acknowledges that the various study designs are subject to bias and other threats to internal validity, even in well designed studies. The Canadian (and subsequently the U.S.) Task Force drew up a classification which was used to grade the quality of study designs and the strength of recommendations for preventive interventions. This hierarchy forms the basis for the critical appraisal of the literature within these bulletins. It provides a way to clarify how well the different types of study can shed light on the risks, benefits and costs of the target intervention.

An intervention that works in a controlled study context such as that provided by a randomized controlled trial may not work in the standard conditions of general practice. The distinction between efficacy and effectiveness is therefore important. While the hierarchy of studies is very valuable as a guideline it is not sufficient. The issue of the wider generalization (external validity) of the study's results needs to be examined. In particular, the effectiveness of an intervention may differ from efficacy due to factors related to the provider and the health care system (costs of care and resources in general), and to the patient (issues of acceptability and compliance to treatment).

Step 3: Searching the literature:

Relevant studies and evidence are gathered together using a structured approach. This activity is coordinated by Oncology Information Service, based at the University of Leeds. This is done in three ways:

  i Initially, the research team and OIS staff explore the full extent of the subject, produce an agreed list of subject keywords and search constraints (for example, limitations by date or country of publication), identify appropriate databases, and match the subject to database thesauri (in the case of *Index Medicus*/**MEDLINE** to *Medical Subject Headings*).
  ii Appropriate external databases and information centres are identified to conduct the initial search, documenting the strategy used and the number of citations retrieved. The strategy is revised and updated in a systematic manner.
  iii Care is taken to ensure that the retrieval of data is cross-disciplinary, to include clinical practice,

health economics, health service management, and inter-sectoral implications.

Whilst this approach successfully locates journal publications, alternative methods are required to achieve a thorough coverage of the literature, some of which may be "semi-published" as "grey" literature in the form of reports of the Royal Colleges, government departmental and Health Authority documents, items published outside the UK, or work in progress.

OIS searches appropriate sources such as indices and catalogues of official publications or the British Library *System for Information on Grey Literature in Europe* (**SIGLE**). External resources are also searched according to the original agreed strategy, including the information units of the Centre for Health Economics (York) and the Information Resource Centre of the Nuffield Institute (Leeds), and the Research Unit of the Royal College of Physicians. Identified clinical experts assist in locating published and unpublished material and to provide information on current and promising research in the topic area, as well as acting as an expert reviewers to the project on matters of a highly technical nature.

Step 4: Reviewing the quality of each study:

Each study requires systematic review. Use is made of well established methodological checklists, based on the approach developed by Sackett *et al.*,[5-8] to identify design strengths and flaws.

Key issues addressed include:

  i internal validity ('Do the results mean what they appear to?'), including in particular the definition of variables and outcomes, their measurement and eventual data quality, the treatment of confounders and sample selection;
  ii statistical power;
  iii the clear specification of the hypothesis prior to inspection of the results, data analysis methods;
  iv and external validity ('Can I generalise?').

In this way the weight of evidence provided by each study is assessed. 'Good' quality studies are extracted for examination against the mapping of the causal pathways, risks and benefits of the target intervention and in the light of the hierarchy of study types.

Step 5: Obtaining an overview of the studies:

Meta-analysis provides a formal way of pooling evidence from a range of studies to form a comprehensive yet usable body of evidence. Prior to any quantitative meta-analysis, a qualitative meta-analysis is undertaken, critically appraising the quality of each of the individual studies. Studies of 'doubtful' validity are down-graded

relative to 'good' studies. There are four stages in this process.

i Where there are several comparable studies examining the efficacy or effectiveness of an intervention a meta-analysis is carried out using formal statistical techniques to provide a single pooled estimate of effect.

ii Because of the range of study designs that is likely to exist for the evaluation of any health care intervention, studies included in the meta-analysis may need to be subdivided to explore observed treatment effects within study design categories.

iii The results from well undertaken meta-analyses are referenced and used.

iv Where appropriate, the overall trend of the treatment effects for each individual study is presented in a tabular or graphic format, together with confidence intervals.

Step 6: Assessing cost effectiveness:

The clinical effectiveness of the health care intervention must be established before a serious investigation of costs can be made.[2] Similar questions on the quality of study design must be asked of the cost-based studies. Use is made of the general approach outlined by Drummond et al.[10] in evaluating published economic appraisals.

In many instances, however, it is anticipated that an economic appraisal may be lacking. Attempts will be made to provide insight into cost implications and point as necessary to the need for further research. Attention will focus not only on the economic consequences for the health services, but also for the community, other sectors and to the patient.

Step 7: Determining acceptability:

Even though a health care intervention has been shown to work, this does not mean that its widespread introduction will have the expected impact. A further dimension for review and assessment is the potential acceptability of the target intervention.

From a clinical perspective, this relates to the notions of compliance and uptake: will patients comply with the treatment regime or attend the screening programme? More broadly, take-up of a service reflects and relates to consumer perceptions of the acceptability of the health care intervention.

Attitudes and perceptions about the clinical condition and side effects of the intervention will affect the demand and utilisation of services. A screening programme may be poorly used because of potential anxiety during and following the intervention (associated, for example, with the question of false positives and false negatives).

Perceptions of health and illness and the experience of illness both in general and for the particular target condition will also affect service uptake, as too will perceptions of the likelihood of cure and the quality of care for the condition.

Evidence on these issues is reviewed in a similar manner to that on effectiveness. Many of the studies on consumer acceptability are in the form of surveys or ethnographic accounts of care and/or of illness. While such studies may not be widely perceived in the medical arena as presenting 'hard' evidence, they must be taken into account in the provision of health care services. If the potential intervention is both clinically and cost effective, the provision of a service that may be poorly used is debatable if compliance is expected to be low. Ways of enhancing the intervention's acceptability must be considered.

Step 8: Judging the overall impact of the intervention:

The final stage in the review and synthesis process is to make an informed judgement of the overall effectiveness and acceptability of the intervention and its likely impact and to identify gaps in knowledge:

i An assessment is made of the balance of risks and benefits: will the intervention do more good than harm? Consideration of possible adverse effects of the intervention are considered, and thus potential increases in the incidence of non-target interventions.[2]

ii The health service context of clinical practice is examined in order to translate the clinical and cost effectiveness recommendations into purchasing policy. Social acceptability, managerial, and intersectoral implications are clarified. Potential and appropriate target groups for the intervention are identified, as far as the evidence allows.

iii The individual and public health impact of the intervention is addressed. Establishing the effectiveness of a procedure does not automatically mean that the overall health of the population is (significantly) improved. Highly effective interventions applied to small high risk groups may have less impact on the nation's health than a more modestly effective intervention for a target condition where there is a greater burden of suffering.

The Bulletins' recommendations:

The key task of the effectiveness bulletins is to separate evidence and interpretation on the basis of informed clinical and other wisdom in order to clarify the effectiveness and acceptability of the target interventions. What emerges are recommendations grounded

in an interpretation of the current evidence following a set of agreed and explicit criteria.

The aim of this analytical process is to provide purchasers and providers with current and scientifically defensible information. The recommendations given in the bulletins are advisory, providing information on the clinical and cost effectiveness and acceptability of the interventions, on the basis of current available evidence. Sound purchasing will require the interpretation of these guidelines in the light of an analysis of the health needs of the local population and social and political factors.

The bulletins are only one means of disseminating the reviews on effectiveness and acceptability, with a further and critical role being played by targeted workshops in order to encourage and facilitate the process of change that may be required. As Jenicek observes, "even if political decisions finally override recommendations, well organised homework is necessary".[9]

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CHARACTERISTICS OF THE SCREENING TEST

The predictive accuracy of a test is measured by its sensitivity (the proportion of women destined to have a fracture, who are correctly identified by the test), specificity (the proportion of women not destined to have a fracture who are correctly identified by the test) and positive predictive value (the proportion of women who are identified as high risk who would go on to have a fracture in the absence of the intervention). A good test will have a high sensitivity and specificity. If the disease is common it will also have a high positive predictive value.

The characteristics of the bone screening test based on a prospective cohort are shown in Table 1.[33] If women with bone mineral content (BMC) in the lowest 20% are identified as being at highest risk this group will contain only 37% of all women who will go on to have hip fractures. Based on a prevalence of hip fracture of 150/1000, the positive predictive value is 28%. That is 28% of women identified as high risk will go on to have a fracture if there is no intervention, hence 72% of women on therapy will not have benefited with respect to preventing a fracture.[15] Alternatively, taking the lowest 40% of BMC will identify 60% of those liable to fracture but using this cut-off the positive predictive value of the test falls to 23% and so 77% of those treated will not have gone on to have a fracture in the absence of treatment.

Table 1
Characteristics of bone mineral content screening test for fracture risk

| | Bone mineral content | |
	Lowest 20%	Lowest 40%
Sensitivity	37%	60%
Specificity	83%	64%

Source: Pitt *et al.*[40]

THE SIDE EFFECTS OF HORMONE REPLACEMENT THERAPY

Hormone replacement therapy is associated with a number of both positive and negative side effects which need to be taken into account in any decision to establish a programme involving HRT.

(a) Coronary heart disease (CHD)
There is evidence that oestrogen alone has some protective effect on heart disease (relative risks of 0.4-0.7 for current use and 0.7-0.9 for past use). However this protective effect is thought to be significantly reduced for combined therapy.[52]

(b) Breast cancer
There have been many studies looking at the risk of breast cancer associated with long term HRT but there is no consensus about any effect. Recent reviews suggest that long term use of oestrogens on their own is associated with a 30% increase in the risk of breast cancer.[52.59] However, studies are difficult to interpret due to the possibilities of selection biases (higher social classes at higher risk of breast cancer are more likely to be taking HRT) and lack of accurate data on HRT dosage and usage. The short follow up period of the studies is also a problem given the long latency period of breast cancer. There is contradictory evidence on the effect of adding progesterone. As with the effect on osteoporosis there is a lack of data on the duration of any effects on the breast beyond the period of treatment. This issue is even further complicated by the contradictory evidence of the effect of HRT on breast cancer fatality rates.

(c) Endometrial carcinoma
There is considerable evidence that oestrogen alone increases the risk of endometrial carcinoma. However this effect disappears when combined therapy is used.[60] Thus women who have not had a hysterectomy are usually advised to receive combined HRT.

(d) Menopausal symptoms
Menopausal symptoms (especially hot flushes) are common and for many women the relief of these symptoms will improve their quality of life. This could be seen as an extra benefit for symptomatic women who are found to be at high risk of fracture. However, there is no evidence that the occurrence of menopausal symptoms is associated with increased risk of fracture. It is also important to distinguish between the treatment of osteoporosis and the alleviation of menopausal symptoms since the nature and the duration of the therapy are different.

(e) Other side effects
One of the negative side effects of combined therapy is the return of menstrual bleeding. This may be a major reason for low short term compliance.

Appendix III

METHODS OF BONE MASS MEASUREMENT

The main techniques for measuring bone density these include: single photon absorptiometry, dual photon absorptiometry (DPA), dual energy X-ray absorptiometry (DEXA) and ultrasound. The newer DEXA method is more precise and takes less time (20 minutes) than the conventional DPA. The precision of DEXA systems is 1-2% and accuracy 3-5%.[29] Ultrasound techniques are relatively new in this area and appear to measure factors affecting bone strength other than bone mass though this technique requires more validation.[30]

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