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Title: A Randomized Controlled Trial of Screening in the Community to Reduce Fractures in Older Women: The SCOOP Study

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Abstract: SUMMARY

Background
Despite effective assessment tools and medications targeting osteoporosis and related fractures, screening for fracture risk is not currently advocated in the UK. We tested whether a community-based screening intervention could reduce fractures in older women.

Methods
We conducted a two-arm randomised controlled trial in women aged 70 to 85 years comparing a screening programme using the FRAX risk assessment tool versus usual management. The primary outcome was the proportion of individuals experiencing one or more osteoporosis-related fractures over a five-year period. In the screening arm, treatment was recommended in women identified to be at high risk of hip fracture, according to the FRAX 10-year hip fracture probability.

Findings
12 483 eligible women, identified from primary care, participated in the trial. Of 6 233 randomised to screening, treatment was recommended in 898 (14.4%). Osteoporosis medication use was higher at the end of year one in the screening group compared to controls (15.3% vs 4.5%, respectively), with uptake particularly higher in the screening high risk subgroup (78.3% at 6 months). Screening did not reduce the incidence of all osteoporosis-related fractures (hazard ratio: 0.94, p=0.178, 95% C.I. : 0.85 to 1.03) but there was strong evidence for a reduction in hip fractures, a pre-specified secondary outcome (hazard ratio : 0.72, p=0.002 95% C.I. : 0.59 to 0.89). There was no evidence of differences in mortality, anxiety levels or health-related quality of life.

Interpretation
A systematic, community-based screening programme of fracture risk in older women in the UK is feasible. Whilst there was no reduction in

overall fracture rate the intervention was effective in reducing hip fractures by an estimated 28%.

Funding
The Arthritis Research United Kingdom (ARUK), formerly the Arthritis Research Campaign (ARC), and the Medical Research Council (MRC) of the UK jointly funded this trial.

A Randomized Controlled Trial of Screening in the Community to Reduce Fractures in Older Women: The SCOOP Study

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Funding

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Introduction

There are approximately 9 million osteoporotic or fragility (low trauma) fractures worldwide per year.[1] In developed nations, around one in three women and one1 in five men aged 50 years or more will suffer a fragility fracture during their remaining lifetime, most commonly at sites such as the hip, distal forearm, vertebrae and humerus. In the UK, around 536 000 people suffer fragility fractures each year, including 79 000 hip fractures, with a cost in 2010 estimated at £3·5 billion expected to rise to £5·5 billion per year by 2025.[2] For the individual, a hip fracture can be devastating with loss of independence and less than one third of patients making a full recovery; mortality at one year post-fracture is approximately 20%.[3]

Advances in osteoporosis management over the last two decades include development of effective low-cost treatments and easily accessible fracture risk assessment tools, such as FRAX®. Bone mineral density (BMD) measurement alone has a relatively low sensitivity for fracture risk and is therefore of limited utility for mass screening;[4,5] the FRAX tool, however, has been shown to increase the sensitivity for fracture risk above that provided by measuring BMD in isolation.[6] Although underpinning many guidelines internationally, no formal studies have prospectively examined the utility of using FRAX to target intervention and reduce fracture incidence.

The aim of the *SCOOP* ('screening for prevention of fractures in older women') trial was to assess the effectiveness of a FRAX-based, community screening programme for UK women aged 70 to 85 years in reducing the incidence of fractures over a five year period.

Methods

Study Design

The *SCOOP* clinical study was a pragmatic, unblinded, two group, parallel, randomised controlled trial to assess the effectiveness and cost-effectiveness of screening to prevent fractures in older women. Details of the methods have been published.[7]

The primary end-point was the proportion of participants experiencing at least one osteoporosis-related fracture, defined in more detail below, over the five-year follow-up. Follow-up data collection points were at 6, 12, 24, 36, 48 and 60 months post-randomisation.

Participants

Participants were recruited in or around seven regions in England: Norwich, Southampton, Bristol, Birmingham, Manchester, York and Sheffield. Women age 70-85 years were identified through primary care lists). Those already on prescription anti-osteoporotic medications (excluding vitamin D or calcium) were excluded; any individuals deemed, by their family doctor, to be unsuitable to enter a research study (e.g. known dementia, terminally ill, recently bereaved, etc.) were also excluded. Where a large number of potential participants were identified, a number were excluded, at random, to ensure for practical reasons that no practice had more than 500 participants.

Written, informed consent was obtained from all participants. At this point, a self-filled questionnaire captured the FRAX risk factors prior to each woman being randomised to the intervention (screening) or control arm. Baseline data comprised age, sex, height and weight for Body Mass Index (BMI) calculation, and dichotomised risk variables including a prior fragility fracture since the age of 50 years, parental history of hip fracture, current tobacco smoking, any long-term

use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis and daily alcohol consumption of ≥3 units daily. If the respondent did not know the answer to an individual question a negative response was assumed.

Randomisation

Allocation to study arm was conducted using blocked randomisation (block length 6), stratified by recruiting region and age group (70 to 74 years, 75 to 79 years and 80 to 85 years). Randomisation was carried out, once relevant data were obtained, using an on-line web-based system. This was set up by an independent data-programmer from the Norwich Clinical Trials Unit. A 1:1 allocation ratio was used.

Intervention Arm

In the screening arm, the baseline risk factor questionnaire was used to calculate the 10-year probability of hip and major osteoporotic fracture using the FRAX risk algorithm.[8] The hip fracture probability was then compared to assessment thresholds for each 5-year age-band (Table 1), as determined previously in an analysis of treatment cost-effectiveness in the UK ,[9] and were classified as low or high risk of fracture. Participants with a low probability received a letter (also notified to their family doctor) confirming their low risk status with a recommendation that no further action was necessary. The remaining participants were invited to undergo a local, DXA-based femoral neck BMD measurement and the 10-year hip fracture probability was recalculated with inclusion of BMD. Height and weight were measured at the DXA visit and the BMI information updated. The presence of rheumatoid arthritis was removed from this calculation as it may have been confused with osteoarthritis by participants and reliance on self-report of rheumatoid arthritis is not recommended for the FRAX algorithm.[10] The final risk category (below or above the age category intervention threshold) was communicated to the participant and family doctor by letter; participants above the threshold were advised to make an appointment with their family doctor to discuss treatment options.

Control Arm

Apart from a letter to the GP informing them of their patient participating in the study, no additional information was provided and they received standard care as usual. The baseline 10-year fracture probabilities, without the inclusion of BMD, were calculated at the end of the trial for comparative purposes only.

Outcomes

The primary outcome was the proportion of participants experiencing at least one osteoporosis-related fracture during the five-year follow-up period. Pre-specified secondary outcomes were the proportions of participants experiencing at least one hip fracture; any clinical fracture; and mortality. The impacts on anxiety (using the State-Trait Anxiety Index (STAI)[11]) and health related quality of life (measured with EQ-5D and SF-12) were also pre-specified secondary endpoints. Family doctors were asked to record any adverse events related to the screening process.

Fracture Ascertainment

Fracture events were captured from a variety of sources. Participants self-reported any fractures occurring since the previous follow-up, including date and anatomical site of fracture, and hospital attended (if any). Routine hospital episode statistics (HES) data[1], comprising information on hospital inpatient stays and emergency department attendance, were interrogated to identify fractures in

any of the study participants from the point of randomisation until the end of follow-up. Primary care records were similarly screened for fractures based upon formal Read codes.

Where self-report or emergency department attendance were the sole source of information, or where there was missing information regarding exact dates or anatomical site of fracture, further verification included requests to primary care practices and searches of radiology records at local hospitals. Vertebral fractures documented within 6 months of randomisation were excluded due to uncertainty over the actual date of occurrence.

Only verified fractures, at any anatomical site, within the five-year follow-up period, were included as outcomes. The level of trauma associated with the incident fracture was not recorded. Incident osteoporosis-related fractures were defined as those excluding the hands, feet, nose, skull or cervical vertebrae. Hip fractures were defined as verified fractures with a specific description of 'neck of femur' or 'proximal femur'. Those described as 'sub-trochanteric', 'femoral shaft', 'distal femur' or simply 'femoral' were not categorised as hip fractures.

Statistical Analysis

Cox's proportional hazards model was used to estimate the hazard ratio between the two study arms for fractures (whether osteoporosis-related, clinical or hip fractures), together with a 95% confidence interval. Recruiting region, baseline FRAX risk value (without BMD, to allow use for control participants) and self-reported falls at baseline were included in the model. These variables were included as prognostic factors and agreed prior to data analysis. Death or withdrawal from the study were treated as censoring events. The same approach was used to compare rates of mortality. The analysis of quality of life data and anxiety data used a general linear model with recruiting region, age and baseline value of the outcome included along with treatment arm at each time point. A repeated measures linear model (with repeated outcome being at the 6 follow-up time points) was also carried out.

All analyses were conducted on an intention-to-treat basis with participants analysed according to the group to which they were randomised, irrespective of whether screening was completed.

Sample Size

The sample size was based upon the ratio of hazard for the two groups for any osteoporosis-related fracture over the follow-up period taking into account the expected recruitment time and expected censored observations due to death. [12] Assumptions included a 2·5% annual incidence of fractures and a death rate of approximately 4·2% per annum in UK women aged 70-85 years.[13,14] Assuming a screening sensitivity of at least 65%, a treatment effect of 35% (i.e. a 35% relative reduction in fractures in individuals on active treatment), and 80% uptake of treatment in the high risk group, a relative reduction in risk of fracture of 18% was estimated, i.e. a hazard ratio of around 0·82. This indicated a sample size of 5790 women per arm would provide 90% power with 5% significance based upon the stated hazard ratio; a fracture rate of 2·0% in the control group would reduce the power to 82%. The target sample size was thus set at 11580, with 5790 per arm.

Ethical Approval and Funding

Full ethical approval was obtained from the North Western - Haydock Research Ethics Committee of England in September 2007 (REC 07/H1010/70). The trial was registered on the International Standard Randomised Controlled Trial Register in June 2007 (ISRCTN 55814835). The Arthritis Research United Kingdom (ARUK), formerly the Arthritis Research Campaign (ARC), and the Medical Research Council (MRC) of the UK jointly funded this trial.

Findings

Participants

Participant progress through the trial is illustrated in Figure 1. A total of 52 033 women aged 70 to 85 years were identified. Following exclusions for concurrent anti-osteoporosis medication use (n=6 927, 13·3%), being deemed unsuitable to enter a research study by their family doctor (n=3 473, 6·7%) or other exclusion reasons (n=3 033, 5·8%; e.g. ensuring no more than 500 participants per practice), letters of invitation were sent to 38 600 women. A further 569 were subsequently excluded when found to be using anti-osteoporosis medication. Of the 38 031 remaining eligible women, 11 068(29·1%) didn't respond (despite a reminder letter) and 13 870 (36·5%) declined to take part. Thus, 13 029 women consented to participate, and a total of 12 495 (32·9% of those eligible) were randomised. The first randomisation was carried out in April 2008 and the last in July 2009. The number of women randomised in each of the seven regions ranged from 1632 to 2055.

Twelve participants were excluded post-randomisation: nine were on anti-osteoporotic medication at randomisation, two were mistakenly entered into the trial twice and one withdrew from the trial post-randomisation. Thus, the results pertain to 12 483 appropriately randomised participants.

Baseline Characteristics

The screening group comprised 6 233 women with 6 250 in the control group. As expected for a randomised trial of this size, the two groups were closely comparable at baseline (Table 2). Compared to those declining participation, participants reported a better education, higher social-economic status, and more frequent histories of previous fracture or parental hip fracture.

Screening Details

Approximately half of those in the screening arm (3 064, 49·2%) were categorised as initial high risk and were invited to have a DXA scan. Of these, 247 (8·1%) did not provide a BMD result (157 declined the invitation, 81 unable to have hip BMD measured and nine died before scan) and consequently did not have an updated fracture risk calculated. Of those with BMD measured at the femoral neck, 898 (14·4% of the screening arm) were deemed to be at high risk after recalculation of their FRAX hip fracture probability (Table 2). The mean femoral neck T-score was -2·6 for this group. The average time from randomisation to notification of risk category in those invited for a DXA scan was 78 days.

Use of anti-osteoporosis medication

By the end of the first year, 953 participants in the screening arm (15·3% of those randomised to the screening arm) had had at least one prescription compared with just 264 (4·5%) in the control arm. Exposure to treatment was higher in those categorised as high risk in the screening arm with 703 (78·3%) having received at least one prescription within 6 months of randomisation. Over the remaining years of follow-up, the proportion on treatment remained fairly constant in the screening arm, at around 13% to 14%, whereas there was a steady increase in treatment exposure in the control arm, with 833 (10·1%) receiving some prescription medication in the final 12 months of follow-up. During the course of the study, around 24% of the screening arm participants received at least one prescription for anti-osteoporosis medication compared with 16% of the control arm.

Efficacy Outcomes

The follow-up period provided 59 401 person-years of observation. Table 3 shows details of the fracture events by group. Overall, 1 975 osteoporosis-related fractures were identified in 1 657 individuals, 13·3% of those randomised. The most common site of fracture was the distal forearm (638 fractures in 614 individuals) followed by the hip (392 fractures in 382 individuals). The estimated rate of new clinical fractures per 100 person years were: overall 3·3, wrists 1·1, hips 0·66.

Over 5 years, the proportion of individuals experiencing an osteoporosis-related fracture (the primary outcome) was similar in the screening arm compared to the control arm (12·9% v 13·6%) with an adjusted hazard ratio (HR) of 0·94 (p=0.178, 95% C.I. : 0·85 to 1·03). A similar result was observed for any clinical fracture (15·3% v 16·0%, HR = 0·94, p=0·183, 95% C.I. : 0·86 to 1·03). In contrast, in a pre-specified secondary analysis, screening led to a relative reduction in hip fractures of 28% compared with usual care (2·6% v 3·5%, HR = 0·72, p=0·002, 95% C.I. : 0·59 to 0·89).

Over 5 years, mortality rates were similar in the screening and control arms (8·8% v 8·4% respectively, HR = 1·05, p=0·436, 95% C.I. : 0·93 to 1·19).

There was no evidence of any impact of screening on anxiety levels (Table 4, p=0·515, repeated measures ANOVA). Those in the high risk group had higher levels of anxiety at baseline, prior to screening, but throughout the study period the mean difference between the high risk group and low risk group, or between the screening and control groups, were extremely small.

We found no evidence of an impact on quality of life assessed by the EQ-5D or SF-12 (Tables 5 and 6).

Discussion

Although the *SCOOP* study did not demonstrate an effect of screening for fracture risk on the primary outcome of any osteoporosis-related fracture, it did lead to a statistically and clinically significant decrease in hip fractures. To the best of our knowledge, this is the first time that a community-screening approach, based upon fracture risk, has resulted in subsequent fracture reductions. Indeed, as recently as 2013, the National Screening Committee of the UK noted an absence of evidence supporting the introduction of screening for fracture risk in postmenopausal women;[15] the one trial of screening identified,[16] commencing in the 1990s, was deemed not to provide sufficiently current evidence.

The SCOOP study has demonstrated the feasibility of a community based, screening programme in women aged 70 to 85 years to reduce hip fractures. The overall screening process was relatively straightforward. Completion of the initial FRAX questionnaire was very good and the DXA scan attendance rate was high; few individuals decided not to, or were unable to, attend for a scan. There was no observed increase in average anxiety levels post-screening and an integrated qualitative study, conducted at the time of the trial, suggested screening was acceptable to both participants and primary care physicians.[17]

There are a number of limitations that need to be considered. Participants represented around only one third of those eligible. There was evidence of a healthy selection bias; for example, the mortality rate over 5 years was less than half of that expected (8·6% versus an expected 19·0%, based upon the age distribution at entry).[14] Those participating also tended be better educated and of a higher socio-economic status than those actively declining. Whilst there is no evidence of a relationship

between socio-economic status or education and fracture risk, only 14% of those screened were deemed at high risk. This is lower than expected with 20% to 40% of post-menopausal women (depending on age) anticipated to be at high risk according to the UK NOGG guidelines.[18] Despite this, the rates of fracture observed were actually higher than anticipated. The expected rates were based upon an epidemiological study from 2001 whose estimates came from primary care Read codes.[13] The discrepancy could be due to a genuine increase in fracture rates since 2001, or an under-estimation based upon the primary care Read coding at the time, or perhaps a combination of the two factors.

Whilst there was no evidence that screening might reduce overall osteoporosis-related fracture incidence, there was strong evidence for a decrease in hip fractures. This discrepancy may be explained by the screening method which used the 10-year risk of *hip* fracture, rather than the risk of *any* major osteoporotic fracture. Whilst the FRAX algorithm can calculate both, and the two risk values are related, they are not perfectly correlated nor interchangeable. Using the hip fracture risk as the screening approach would, of course, be more sensitive to predicting, and therefore better at preventing, hip fractures, rather than fractures at other sites. This is likely to explain the discrepancy seen.

The absolute size of decrease in hip fracture rates was 0·9%, requiring 111 individuals to be screened in order to avert one hip fracture. The relative risk reduction of 28%, though somewhat less than the 40% reduction observed in clinical trials of osteoporosis medication, is substantial given the absence of treatment in the greater majority of the screening group and treatment for a proportion of the controls. While it is possible that the reduction was due to more than just an effect of prescribed medication, for example the process may have influenced behaviour to reduce hip fractures in a selected group more open to the influence of risk information, there is little evidence that provision of simple health-related information can substantially reduce fracture risk ; studies addressing strategies to reduce fall risk, for example, have not been associated with significant decreases in fracture risk.[19]

In conclusion, despite no overall reduction in fractures, this trial has demonstrated that community screening, based upon the FRAX probability of hip fracture, leads to a significant reduction in hip fractures in older women. Cost-effectiveness analyses are ongoing but the SCOOP study provides promise of an effective community-based management strategy in the UK, and elsewhere, to reduce hip fractures.

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The 'SCOOP Study Team' consists of the authors and the following researchers who worked directly on the SCOOP study

Birmingham : Nicola Crabtree, Helen Duffy, Jim Parle, Farzana Rashid, Katie Stant
Bristol : Kate Taylor, Clare Thomas (nee Emmett)
Manchester : Emma Knox, Cherry Tenneson, Helen Williams
Norwich: David Adams, Veronica Bion, Jeanette Blacklock, Tony Dyer
Sheffield : Selina Bratherton (nee Simpson), Matt Fidler, Katharine Knight, Carol McGurk, Katie Smith, Stacey Young
Southampton : Karen Collins, Janet Cushnaghan
York : Catherine Arundel, Kerry Bell, Laura Clark, Sue Collins, Sarah Gardner, Natasha Mitchell

Contributions

EL was responsible for the organisation and co-ordination of the trial. LS was the Chief Investigator and also responsible for the data-analysis. LS, CC, SC, RF, NG, IH, AH, RH, AHo, JK, TM, TO, TP, DT and EM developed the trial design. All authors contributed to the writing of the final trial manuscript. All members of the *SCOOP Study Team* contributed to the management or administration of the trial.

Declarations of Interest

Professor N Harvey has received consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Consilient Healthcare and Internis Pharma

Professor McCloskey has been, or currently is, an advisor or speaker for ActiveSignal, Amgen, AstraZeneca, Consilient Healthcare, GSK, Hologic, Internis, Lilly, Medtronic, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Synexus, Tethys, UCB, Warner Chilcott. He has also received research support from these plus I3 Innovus, the IOF and Unilever.

Professor Kanis has held grants from Amgen, Lilly, Unigene and Radius Health; non-financial support from Medimaps, Asahi and AgNovos; Professor Kanis is the architect of FRAX but has no financial interest

Professor Cooper Cooper has received consultancy fees and honoraria from Amgen, Danone, Eli Lilly, GSK, Medtronic, Merck, Nestle, Novartis, Pfizer, Roche, Servier, Shire, Takeda and UCB.

No other declarations of interest are reported.

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REFERENCES

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006;17: 1726–33.
2. Hemlund E, Svedbom A, Ivergard M et al. Osteoporosis in the European Union : medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation and the European Federation of Pharmaceutical Industry Associations. *Arch Osteoporos* 2013;8:136.
3. Sernbo I, Johnell O. Consequences of a hip fracture: a prospective study over 1 year. *Osteoporosis Int* 1993;3: 148–53.
4. Schuit SCE, van der Klift M, Weel AEA, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone* 2004;34:195-202.
5. Wainwright SA,Marshall LM, Ensrud KE, et al. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab* 2005;90:2787-93.
6. Kanis JA, Oden A, Johnell O et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007;18:1033-1046.
7. Shepstone L, Fordham R, Lenaghan E, et al. A pragmatic randomised controlled trial of the effectiveness and cost-effectiveness of screening older women for the prevention of fractures: rationale, design and methods for the SCOOP study. *Osteoporos Int* 2012;23:2507-2515.

8. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporos Int* 2008;19: 385-397.
9. Kanis JA, Borgstrom F, Zethraeus N, et al. Intervention thresholds for osteoporosis in the UK. *Bone* 2005;36:22-32.
10. https://www.shef.ac.uk/FRAX/tool.jsp Accessed 28-10-2016.
11. Spielberger, CD, Gorsuch, RL, Lushene, R, Vagg, PR, Jacobs, GA (1983) Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press
12. Lakatos E, Lan K. A comparison of sample size methods for the log-rank statistic. *Stats Med* 1992; 11:179-191
13. van Staa, TP, Dennison, EM, Leufkens, HGMet al. Epidemiology of fractures in England and Wales. *Bone* 2001;29:517–522.
14. Deaths Registered in England and Wales. Released November 2015. Available at http://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathsregisteredinenglandandwalesseriesdrreferencetables Accessed 28-10-2016.
15. Screening for osteoporosis in postmenopausal women. UK National Screening Committee. March 2013. Available at http://legacy.screening.nhs.uk/osteoporosis Accessed 28-10-2016.
16. Barr RJ, Stewart A, Torgerson DJ, et al. Population screening for osteoporosis risk: A randomised controlled trial of medication use and fracture risk. *Osteoporos Int* 2010; 21:561-568.
17. Emmett CL, Redmond NM, Peters TJ, et al. Acceptability of screening to prevent osteoporotic fractures: A qualitative study with older women. *Family Practice* 2012;29:235-242.
18. Compston J, Cooper A, Cooper C, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. *Maturitas*; 62:105-108.
19. Silva RB, Eslick GD, Duque G. Exercise for falls and fracture prevention in long term care facilities: A systematic review and meta-analysis. *J Am Med Dir Assoc* 2013;14:685-689.

Age Group	*BMD Threshold*	*Treatment Threshold*[1]
70-74	5.18%	5.24%
75-79	6.81%	6.87%
80-84	8.46%	8.52%
85	8.39%	8.99%

1: Post-BMD measurement

Table 1: Risk Thresholds for invitation for BMD Measurement and Treatment

		Non-participants (N=15097)[1]	*Control (N=6250)*	*Screening (N=6233)*	*Screened High Risk (N= 898)*
Has a degree?	*Yes*	1080 (9.9%)	1266 (20.3%)	1270 (20.4%)	182 (20.3%)
Social Class	*I*	570 (5.8%)	641 (10.3%)	615 (9.9%)	86 (9.6%)
	II	2206 (22.4%)	1827 (29.2%)	1871 (30.0%)	266 (29.6%)
	IIIN	1651 (16.8%)	1094 (17.5%)	1015 (16.3%)	211 (23.5%)
	IIIM	3196 (32.5%)	1626 (26.0%)	1622 (26.0%)	163 (18.2%)
	IV	1476 (15.0%)	718 (11.5%)	1471 (12.1%)	112 (12.5%)
	V	739 (7.5%)	244 (3.9%)	250 (4.0%)	38 (4.2%)
Ethnic group	*White*	10955 (98.4%)	6160 (98.6%)	6157 (98.8%)	893 (99.4%)
	Black	66 (0.6%)	26 (0.4%)	26 (0.4%)	1 (0.1%)
	Asian	65 (0.6%)	18 (0.3%)	25 (0.4%)	3 (0.3%)
	Other	47 (0.4%)	23 (0.4%)	15 (0.2%)	1 (0.1%)
Fallen in past year?	*Yes*	2186 (19.9%)	1700 (27.2%)	1744 (28.0%)	295 (33.0%)
Broken bone since 50?	*Yes*	1859 (17.0%)	1463 (23.4%)	1399 (22.4%)	409 (46.0%)
Parents broken hip?	*Yes*	536 (5.3%)	577 (9.2%)	585 (9.4%)	354 (41.6%)
Smoker?	*Yes*	826 (7.4%)	290 (4.6%)	290 (4.7%)	86 (9.6%)
Moderate Drinker?	*Yes*	383 (3.4%)	225 (3.6%)	219 (3.5%)	60 (6.7%)
Glucocorticoid Use?	*Yes*	--	312 (5.0%)	316 (5.1%)	113 (13.3%)
Rheumatoid Arthritis?	*Yes*	--	410 (6.6%)	426 (6.8%)	79 (9.3%)
Secondary Causes of OP?	*Yes*	--	1408 (22.5%)	1483 (23.8%)	267 (29.7%)
Age (at response)	*Mean (SD)*	76.8 (5.84)	75.5 (4.14)	75.4 (4.16)	77.2 (4.40)
BMI	*Mean (SD)*	26.1 (4.90)	26.7 (4.75)	26.7 (4.71)	24.4 (4.06)
FRAX 10 year HIP Fracture Probability[2]	*Mean (SD)*	--	8.5% (7.3%)	8.5% (7.4%)	17.9% (10.9%)
FRAX 10 year Major OP Fracture Probability[2]	*Mean (SD)*	--	19.3% (8.8%)	19.3% (8.9%)	30.0% (10.7%)

1: Percentages are of those providing a non-missing answer.

2: Prior to BMD results.

Table 2 : Baseline Characteristics

	Control (N=6250)	*Screening (N=6233)*	*Relative Risk (95% C.I.)*	*Hazard Ratio[1] (95% C.I.)*
OP-Related				
No Fracture	5398	5428		
Fracture	852 (13.6%)	805 (12.9%)	0.95 (0.87 , 1.04)	0.94 (0.85 , 1.03) p=0.178
Hips				
No Fracture	6032	6069		
Fracture	218 (3.5%)	164 (2.6%)	0.75 (0.62 , 0.92)	0.72 (0.59 , 0.89) p=0.002
All Clinical				
No Fracture	5248	5282		
Fracture	1002 (16.0%)	951 (15.3%)	0.95 (0.88 , 1.03)	0.94 (0.86 , 1.03) p=0.183
Mortality				
Survive	5725	5683		
Died	525 (8.4%)	550 (8.8%)	1.05 (0.93 , 1.18)	1.05 (0.93 , 1.19) p=0.436

1: Adjusted for Recruiting Region, Baseline FRAX Probability and Falls.

Table 3 : Efficacy Outcomes

	Low Risk (N=5088)	*High Risk (N= 898)*	*Control (N=6250)*	*Estimated Difference*[1]	*p-value*[2]
Baseline	10.1 (3.65)	10.5 (3.73)	10.2 (3.68)	-	-
6 Months	10.2 (3.78)	10.2 (3.74)	10.2 (3.67)	0.045	0.961
12 Months	10.2 (3.71)	10.3 (3.91)	10.2 (3.70)	-0.085	0.809
24 Months	10.2 (3.71)	10.4 (3.76)	10.2 (3.76)	-0.154	0.562
36 Months	10.3 (3.73)	10.5 (3.87)	10.3 (3.73)	-0.081	0.756
48 Months	10.4 (3.78)	10.4 (3.68)	10.4 (3.75)	-0.093	0.647
60 Months	10.5 (3.83)	10.6 (3.70)	10.4 (3.81)	-0.184	0.226
			Repeated Measures Analysis	*Group*[3]	0.515
				*Group*Time*[4]	0.942

1: Control – High Risk, adjusted for Recruiting Region, Age and Baseline STAI.

2: Test of any group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 4 : State-Trait over five years follow-up, Mean (SD)

	Intervention (N=6233)	*Control (N=6251)*	*Estimated Difference*[1]	*p-value*[2]
Baseline	0.74 (0.24)	0.74 (0.23)	-	-
6 Months	0.74 (0.24)	0.74 (0.24)	-0.003	0.394
12 Months	0.74 (0.25)	0.73 (0.25)	-0.010	0.020
24 Months	0.71 (0.27)	0.72 (0.26)	-0.003	0.537
36 Months	0.68 (0.29)	0.69 (0.28)	-0.006	0.273
48 Months	0.67 (0.31)	0.66 (0.30)	-0.008	0.154
60 Months	0.63 (0.33)	0.63 (0.32)	-0.003	0.642
		Repeated Measures Analysis	*Group*[3]	0.154
			*Group*Time*[4]	0.586

1: Control – Intervention, adjusted for Centre, Age and Baseline EQ-5D

2: Test of group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 5 : EQ-5D over five years follow-up (Deaths imputed to zero).

	Intervention (N=6233)	*Control (N=6250)*	*Estimated Difference*[1]	*p-value*[2]
Baseline	45.0 (10.5)	45.3 (10.2)	-	-
6 Months	44.8 (10.8)	44.8 (10.7)	-0.26	0.087
12 Months	44.5 (11.3)	44.6 (11.3)	-0.23	0.182
24 Months	43.0 (12.7)	43.3 (12.4)	-0.06	0.753
36 Months	41.6 (14.1)	41.7 (13.9)	-0.22	0.349
48 Months	40.1 (15.5)	40.1 (15.3)	-0.26	0.317
60 Months	38.3 (16.7)	38.3 (16.6)	-0.20	0.481
		Repeated Measures Analysis	*Group*[3]	0.237
			*Group*Time*[4]	0.881

1: Control – Intervention, adjusted for Centre, Age and Baseline SF-12.

2: Test of group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 6(a): SF-12(Physical Health) over five years follow-up (Deaths imputed to zero).

	Intervention (N=6233)	*Control (N=6250)*	*Estimated Difference*[1]	*p-value*[2]
Baseline	53.1 (8.5)	53.1 (8.5)	-	-
6 Months	52.4 (9.5)	52.2 (9.5)	-0.24	0.164
12 Months	51.8 (10.3)	51.6 (10.3)	-0.17	0.382
24 Months	50.8 (12.3)	51.1 (11.9)	0.29	0.210
36 Months	49.4 (14.3)	49.6 (14.3)	0.07	0.805
48 Months	47.9 (16.4)	47.9 (16.3)	0.19	0.535
60 Months	46.0 (18.3)	46.3 (18.2)	0.56	0.103
		Repeated Measures Analysis	*Group*[3]	0.554
			*Group*Time*[4]	0.056

1: Control – Intervention, adjusted for Centre, Age and Baseline SF-12.

2: Test of group difference

3: Repeated Measures ANOVA test of between group difference

4: Repeated Measures ANOVA test of group by time interaction

Table 6(b): SF-12(Mental Health) over five years follow-up (Deaths imputed to zero).

31st January 2013 Version 2.4

CLINICAL STUDY PROTOCOL

A pragmatic randomised controlled trial of the effectiveness and cost effectiveness of screening for osteoporosis in older women for the prevention of fractures – The 'SCOOP' Study

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Summary

Osteoporotic, or low-trauma, fractures – in particular hip fractures – present a considerable burden to the National Health Service and, to the individual, have major adverse effects on quality of life in terms of pain and disability. Around 50% of hip fracture patients lose the ability to live independently and 20% die within a year of their fracture; one-quarter of the excess is attributable to the fracture itself, rather than pre-existing co-morbidity.

Given the availability of treatments of demonstrated efficacy and a potential screening tool based upon clinical risk factors and bone mineral density (the WHO risk algorithm), a *prima facie* case exists to undertake a community-based controlled evaluation of screening for subjects at high risk of osteoporotic fractures.

This study, following on from an 18 month feasibility study, is a UK 7 centre, unblinded, pragmatic, randomised controlled trial lasting 87 months with a minimum of 5 years follow-up. A total of 11 580 women, aged 70 to 85 and not currently on prescription medication to prevent osteoporotic fractures, will be consented to the trial by post via primary care. This will provide 90% power to detect an 18% decrease in fractures.

Upon receipt of valid baseline data, participants will be randomised to either a screening arm or control arm. Those in the screening arm will have a 10-year fracture probability computed from baseline risk factors together with bone mineral density measured *via* a DXA scan in selected subjects. Individuals above an age-dependent threshold will be recommended for treatment (typically an oral bisphosphonate) to continue treatment for the duration of the trial. The risk of fracture will not be calculated for subjects in the control arm, who will receive "usual care".

Study subjects will be followed-up at 6 months after randomisation and annually by postal questionnaires and checking of hospital radiology and admissions records plus primary care sources. The primary outcome measure will be the proportion of individuals sustaining fractures in each group; hip fracture rate will be a secondary outcome measure. An economic analysis will be carried out to assess cost-effectiveness. A qualitative evaluation will also be conducted to examine the acceptability of the DXA scanning and risk assessment process to participants.

1. Study Identifiers

1.1 Full title of trial

A pragmatic randomised controlled trial of the effectiveness and cost effectiveness of screening for osteoporosis in older women for the prevention of fractures.

1.2 Acronym (only if applicable - this is not a requirement)
'SCOOP' – **Sc**reening **O**f **O**lder women for **P**revention of fracture

1.3 ISRCTN

55814835

2. Study Background

2.1 The problem to be addressed

Osteoporosis is defined as a systemic skeletal disease characterised by compromised bone density and quality, predisposing to an increased risk of fracture [1]. Definitive clinical diagnosis requires measurement of bone mineral density (BMD). The current reference diagnostic standard is dual-energy x-ray absorptiometry (DXA) of the femoral neck [2].Osteoporosis is conventionally diagnosed when BMD values lie 2.5 standard deviations or more below the young adult reference age, a T-score less than -2.5 SD. Studies suggest that about 20% of all western women over the age of 50 years have osteoporosis and that the prevalence increases exponentially with age [3].

The clinical significance of osteoporosis rests with the increased fracture risk and the consequent increased morbidity and mortality. Within Europe, osteoporotic fractures account for almost 2% of the burden of non-communicable disease and are associated with more disability adjusted life-years (DALYs) than common cancers, with the exception of lung cancer. The DALYs lost in Europe due to osteoporosis (2.0 million) are greater than for rheumatoid arthritis (1.0 million) [4]. Osteoporosis increases the risk of bone fracture at all sites, but typical 'low-trauma' fractures occur at the distal forearm, the vertebrae and the hip. It has been estimated that nearly one woman in two will experience an osteoporosis related fracture following menopause [5]. More than 200 000 fractures occur in the UK each year as a direct result of osteoporosis [6]. These fractures have major adverse effects on quality of life in terms of pain and disability and around 50% of hip fracture patients lose the ability to live independently [7]. Furthermore 20% die within a year of their fracture [8]; one-quarter of the excess is attributable to the fracture itself, rather than pre-existing co-morbidity. The average stay in hospital is 27 days and hip fractures account for more than 20% of all orthopaedic bed occupancy. Each year the estimated 70,000 hip fractures in the UK cost health and social services £1.7 billion [9]. With an aging population, the cost to society and individuals of treatment, rehabilitation and premature mortality is set to increase.

Interventions to reduce fracture risk
There is compelling evidence that pharmacological interventions, such as hormone replacement therapy (HRT), vitamin D and calcium, strontium ranelate or bisphosphonates, can significantly decrease the incidence of osteoporotic fractures [10] [11] [12] [13] [14] [15]. Studies of bisphosphonates in osteoporotic women suggest an estimated reduction in vertebral fracture risk of around 50% [14], [15], a reduction in non-vertebral fractures of 20-30% and a global risk reduction of approximately 35% for all fractures.

At or around the menopause, however, there are uncertainties concerning the ultimate impact of, say, 5-10 years of intervention on fracture risk in later life. Most epidemiological information indicates that, whereas the risk of fracture is reduced in women taking HRT, for example, the effect appears to wane over a period of 15-20 years. Thus, interventions offered around the time of the menopause are likely to have little or no effect at the age of,

say, 70 years when the risk of fracture begins to increase most sharply. There is increasing evidence that the impact of treatment would be greater if started at a later age. In a Health Technology Assessment review of the treatment of established osteoporosis, where intervention thresholds were based on a cost utility cut-point of £20,000/QALY, several treatments including calcium, HRT and bisphosphonates were found to be cost-effective when used in individuals with osteoporosis aged 70 years or older [16]. Further, if one assumes that 25% of women in this age group have a relative risk of 2 or greater and that treatment is 50% effective, then fracture incidence could be decreased by between 23% and 26% [16]. It is reasonable therefore to propose that the identification of fracture risk in older women followed by appropriate treatment of proven effectiveness could substantially reduce fracture incidence.

Screening strategies
The role of BMD as a predictor of future fracture risk is well established. Many cross-sectional and prospective studies demonstrate a 1.5-2.5 fold increased risk of fracture for every standard deviation decrease in BMD [17]. The predictive ability of BMD for future hip fracture is comparable to that of blood pressure measurement for stroke and better than that of serum cholesterol measurements for cardiovascular disease.

However, BMD measures show poor sensitivity for future fracture. Even assuming a 2-fold increase in risk for each standard deviation decrease in BMD, the sensitivity remains below 50% over most reasonable assumptions, i.e. over half of those who suffer fractures would not be identified as at risk. Recent empirical evidence has demonstrated the low sensitivity of BMD alone in the prediction of fractures. In a Rotterdam based study [18] only 44% of women suffering a non-vertebral fracture over an average follow-up of 6.8 years had a T-score of less than -2.5 SD; over 12% had normal BMD levels. A study from the US [19] found only 46% of women suffering a hip fracture over a 5 year period had T-scores less than -2.5 SD at baseline. Thus, if treatment is based solely upon BMD many women at high risk that would benefit from treatment, perhaps the majority based upon a T-score threshold of -2.5, would not be identified as such. Based upon its low sensitivity and also for reasons of cost and accessibility, the Royal College of Physicians' (RCP) guidelines on the prevention and treatment of osteoporosis, produced in 1999, recommended that DXA measurements be used in a case-finding strategy rather than used for general screening [6].

The relatively low sensitivity partly reflects the multi-factorial causality of fractures and the influences of BMD-independent risk factors both within and external to the skeleton. The WHO Collaborating Group at Sheffield is coordinating a meta-analysis of independent risk factors for fracture from 8 prospective international cohorts including a recent Sheffield cohort. In this analysis of approximately 45,000 men and women, the following risk factors have been investigated: age, prior fragility fracture, low BMI, prior corticosteroid exposure, a family history of fragility fracture, secondary causes of osteoporosis (e.g. rheumatoid arthritis), very low calcium intake, smoking and alcohol [20]. It is important to note that this strategy has not incorporated risk factors such as stroke or falls that may not be amenable to the interventions to be used in this study. The combination of clinical risk factors with BMD provides a more accurate assessment of risk than is possible with BMD alone and therefore substantially increase the sensitivity (up to approximately 70% depending on the gradient of risk and the proportion of the population deemed to be at high risk) without significantly impairing specificity [16]. More women would be appropriately treated and the potential to reduce fracture rates improved.

The validity of clinical scoring systems in predicting future fracture risk has been demonstrated [21] [22] [23] and the collaborating centre at Sheffield has validated the utility of integrating risk factors in independent cohorts with more than 1 million patient years of observation [24]. A strong case can be made, therefore, for evaluating a screening strategy which combines a self-completed risk assessment questionnaire followed subsequently by DXA to refine risk estimation where necessary. A further major attraction of an initial self-completed clinical risk factor approach is its ease and low cost of application and hence the likely high uptake rate. DXA BMD measurement would, in such a strategy, only be used in a targeted fashion thus reducing costs.

By incorporating the hazard of fracture with the hazard of death over a ten year period an absolute 10-year probability of fracture can be estimated [25] [26], providing a simple metric against which intervention thresholds can be established. The use of an absolute risk rather than a relative risk for establishing intervention thresholds has been argued for on the basis of numerous advantages [27]. Similar approaches have been used in the management of cardiovascular diseases where smoking, blood pressure, diabetes and serum cholesterol are used to identify patients at high risk.

A possible counterargument to the evaluation of risk in the absence of BMD measures is that studies of efficacy have largely been undertaken in individuals with known low BMD. Treatment may not, therefore, be as effective when prescribed on the basis of a non-BMD risk assessment. For example, the efficacy of risedronate could not be demonstrated in women over the age of 80 selected primarily on their risk of falling [14]. However, many clinical risk factors also influence BMD and can identify sub-populations with low BMD [26]. Furthermore, empirical data from several studies demonstrate that anti-resorptive therapy achieves similar relative risk reduction across a range of BMDs including raloxifene, [28] risedronate [29], alendronate [30] and strontium ranelate [12].

2.3 The need for a trial

The prevalence of, and awareness of, osteoporosis is increasing. Given the magnitude of the public health problem posed by osteoporotic fractures – in particular hip fractures – and the existence of acceptable screening modalities and acceptable treatments of demonstrated efficacy (in terms both of slowing or reversing decline in bone density and in terms of reducing fracture rates), a *prima facie* case now exists to undertake a formal but realistic community-based controlled evaluation of screening for subjects at high risk of osteoporotic fractures. There is a large information gap in this area; there has never been, for example, any formal assessment of the RCP guidance published in 1999.

Although many of the Wilson and Jungner [31] criteria for screening may already be judged to be met, the overall cost effectiveness of a screening program will be determined by the ease and acceptability of the screening "test" (and hence the uptake rate), alongside the ability of the assessment to predict fracture risk, the effectiveness of treatment and the cost of the program.

Given the proposed screening modality (initial clinical risk approach augmented selectively by BMD measurement), treatments of newly demonstrated efficacy, and the target age group (older rather than peri-menopausal) together with some evidence from empirical studies (see below) it would appear timely to propose a large scale controlled empirical examination of the potential effectiveness of an offer of screening to the older female population. An adequately powered randomised controlled trial is of critical importance to determine whether the predicted benefits of screening and treatment are observed in a general setting.

Further, the guidelines published by the National Institute for Clinical Excellence in January 2005 [32] on secondary prevention of fragility fractures in postmenopausal women stated the need to consider the identification of women at risk using risk factors other than age and BMD.

An 18 month feasibility study commenced in April 2005 in Norwich and Sheffield, and has now been completed. This was funded by a £200 000 grant from the Arthritis Research Campaign (**arc**). Over 500 subjects were recruited into the study from 15 different primary care practices. The resulting data have informed the design of the main trial, particularly providing accurate data for a sample size calculation and costs and demonstrating the logistical feasibility.

No systematic review has been published of screening for osteoporosis but a systematic review of the literature has been carried out. In the US, where screening for osteoporosis in

women over the age of 65 has become standard practice, just one clinical trial of screening has been published [33]. This was not, however, a trial of screening versus non-screening but a trial of 3 different screening strategies. In the UK, just two clinical studies of screening for osteoporosis have been identified. The first, carried out in Aberdeen in 1993 examined concordance with HRT use in peri-menopausal women after a DXA scan [34]. The second, the only randomised controlled trial of screening for osteoporosis identified, also carried out in Aberdeen, considered women aged 70 years and older [35]. This study used a simple clinical tool completed by study subjects at their GP surgery combined with ultra-sound measurements. Those considered at high risk were prescribed calcium and vitamin D supplements and given advice on falls prevention. The primary endpoint was the number of falls experienced over a three year follow-up and fractures sustained was a secondary endpoint. This study demonstrated the applicability of screening in this population, in terms of subjects' participation. There was a decreased number of falls in the screening group and a 50% decrease in fractures. However, this trial did not use BMD measures, fracture was not the primary outcome measure and no economic analysis was performed.

2.3 Principal research questions

The primary research question is whether a community based screening program for osteoporosis reduces the incidence of fractures, and is cost-effective, in older women. Secondarily, the study will assess, using a qualitative approach, the acceptability of the screening process to participants.

The results from the trial will make a critical and timely contribution to the evidence-base regarding the introduction of a nationally organised screening program.

2.4 Study risks

The trial does not involve new medicinal products or any invasive or potentially harmful procedures and is considered low risk for participants.

The only risks directly related to the screening process come from the exposure to radiation from the DXA scan and the psychological impact of being declared at high risk of fracture from the screening process. The former is negligible. A DXA scan of the femoral neck is no more than 0.02 mSv, equivalent to 3 days background radiation, and substantially less than a standard hip x-ray (0.7 mSv). One study [36] considered the psychological impact of being at high risk of osteoporotic fracture, based upon a low BMD score. This study concluded that general anxiety in women with a low BMD score 3 months after the scan was similar to that 2 weeks prior. Those without a low BMD score had lowered anxiety (about half a standard deviation) in comparison. Another study, using qualitative methods, however, suggested that women informed of a higher risk were left feeling more uncertain and restricted than previously [37]. It is intended, therefore, to consider stress and anxiety caused by screening as a formal part of the proposed clinical trial using both self report quantitative and qualitative data.

As with any screening program there may be the risk of anxiety over a 'positive' result but all participants deemed at risk of fracture will be notified to their GP who will be able to discuss therapeutic intervention options.

The main risk to the trial comes with the possibility of low recruitment. However, there is a degree of flexibility in the recruitment procedure to allow for shortfalls at early stages to be made up later. Also, the feasibility study that has been run has provided sound evidence upon which recruitment rates have been based.

Ascertainment of the primary outcome measure does not rely wholly on the actions of study participants (fractures can still be ascertained despite non-response), and therefore follow-up data should be very good.

3.Trial Design

3.1 Trial Outline

The study has been designed as a multi-centre, unblinded, pragmatic, randomised controlled trial lasting 87 months, comprising a 9 month 'pre-trial' period, 16 month recruitment and screening period, 60 month treatment/follow-up period (over-lapping with the recruitment and screening) and a final 6 month analysis and dissemination period. The key phases of the trial are shown in Figure 1.

A total of 11 580 women aged 70 to 85, recruited for reasons of generalisability and capacity from seven separate geographical areas within England, will be consented to the trial by post and asked to complete a baseline questionnaire including demographic and clinical variables.

Upon receipt of valid baseline data, participants will be randomised to either a screening arm or control arm. Those in the screening arm will have a 10-year fracture risk computed from the baseline information followed by bone mineral density measured *via* a DXA scan in selected subjects. If an individual's risk lies above an agreed, age-dependent threshold the subject's GP will be recommended to consider introducing treatment (treatment recommendations based on current best evidence will be offered, currently an oral bisphosphonate) and continuing treatment for the duration of the trial. The risk of fracture will not be calculated for subjects in the control arm who will receive "usual care".

All trial subjects will be followed-up at 6 months post-randomisation and then annually by postal questionnaires, plus checking of hospital radiology and admissions records and primary care sources. The primary outcome measure will be the proportion of individuals sustaining fractures in each group; hip fracture rate will be a secondary outcome measure. An economic analysis will be carried out to assess cost-effectiveness.

A qualitative evaluation will be conducted to examine the acceptability of the DXA scanning and risk assessment process to participants.

3.2 Trial interventions

Subjects in the intervention screening arm of the trial will have a ten year risk of fracture calculated from a WHO risk algorithm. This is based upon questionnaire data and, for some subjects, results from a DXA scan [26]. The WHO algorithm is calibrated to the epidemiology of the country, and the impact of risk factors on mortality is also incorporated. Based on this information, a recommendation to consider treatment or not will be communicated to subjects' GPs.

The fracture probability will be calculated from the reported individual details. These comprise age, sex, weight (in kg) and height (in cm). Body Mass Index (BMI) is automatically computed from height and weight (kg/m^2). Dichotomised risk variables are: a prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever long-term use of corticosteroids, rheumatoid arthritis, other causes of secondary osteoporosis and daily alcohol consumption of ≥3 units daily. If responses are missing, subjects will be contacted to obtain the required information. If the subject does not know the answer to an individual fracture risk question, a negative response will be assumed.

A 10-year probability of hip, clinical spine, shoulder or wrist fracture and also a 10-year probability of hip fracture alone are then calculated based upon this information. This former probability is then compared to an intervention threshold for each 5-year age-band (see table 1) at which treatment is cost-effective based on data from within the UK [38]. Subjects with a low probability relative to the threshold, and their GPs, will receive a letter confirming their low risk status and no further action will be taken. The remaining subjects will be invited to undergo a BMD assessment (using DXA) and the fracture probability

recalculated following inclusion of the femoral neck BMD (as a T-score). Following this, the final category (below or above treatment threshold) will be communicated to the subject and GP by letter. Those subjects above the treatment threshold will be asked to make an appointment with their GP (or appropriate health care professional in the practice) to discuss treatment options.

Table 1: Risk Thresholds for BMD Measurements and Treatment

Age Group	BMD Threshold	Treatment Threshold
70-74	5.18%	>5.24%
75-79	6.81%	>6.87%
80-84	8.46%	>8.52%
85	8.39%	>8.99%

At 3 months after this letter has been sent, study subjects above the treatment threshold will be contacted by phone and asked whether or not they have yet seen their GP. If they have not, they will be encouraged to visit their GP in order to discuss treatment options. A follow-up letter will also be sent. Those subjects that have already seen their GP will be asked if they have been prescribed treatment and whether or not they are taking that treatment. If a negative response is given, the benefits of taking the treatment will be described and the study subject will be encouraged to speak to their GP again if they are experiencing any difficulties with treatment. A follow-up letter will again be provided.

There are likely to be women in the intervention group who will not be concordant with screening (although data from the pilot study suggests that this number is very small – only 1 person of 66 in Norwich failed to keep a DXA appointment) or non-adherent with treatment if deemed necessary. However, this is part of the pragmatic nature of the study and the effectiveness of a screening program, which is being estimated, would be dependent upon concordance. Treatment adherence will be investigated at follow-up as a process measure.

The control group will have the same initial risk data collected by questionnaire but their risk will not be calculated nor communicated to their GP until the study is completed and used only to consider baseline comparability. Both experimental and control groups will be provided with lifestyle advice through an **arc** booklet on osteoporosis.

3.3 Duration of treatment period

The screening process involves up to two stages (baseline questionnaire and DXA) with up to one reminder/further appointment sent for each stage. This process will be completed within 6 months of randomisation. The screening process will take place only once during the trial. The recommended treatment duration for women found to be above the fracture risk threshold will be the duration of the follow-up period, i.e. 5 years. Termination of treatment at the end of the study will be at the GP's discretion.

3.4 Study Subject Selection

Study subjects will be selected from the general community after identification via primary care. The following entry criteria will be used :

Inclusion :

- Female
- Aged 70 to 85 years inclusive
- Providing informed consent and necessary baseline information.

Exclusion :

- Known to be on prescription treatment for osteoporosis (other than calcium and vitamin D)
- Any known co-morbidity that would in the GP's opinion make entry to the trial inadvisable (for example advanced malignancy)

- Other factors that would make invitation to participate to a research study inappropriate (e.g. recent bereavement).

3.5 Sample size calculations

The sample size is based upon the ratio of hazard for any fracture over the follow-up period of 5 years between the two groups, taking into account the recruitment period and expected drop outs due to death [39].

Within this age group, an epidemiological study [40] of fracture rates in England and Wales indicates an incidence of between 2.0% and 2.5% *per annum*. National statistics suggest a death rate of approximately 4.2% *per annum* in females in this age group. Assuming a treatment effect of 35%, a sensitivity of at least 65% and 80% uptake of recommended treatment, a realistic relative reduction in risk of fracture would be around 18%, i.e. a hazard ratio of 0.82. Assuming a fracture rate of 2.5% *per annum* in the control arm these data indicate a sample size of 5790 women per arm would provide 90% power with 5% significance based upon the stated hazard ratio; a fracture rate of 2.0% in the control group would reduce the power to 82% for the same sample size.

The recently run pilot study in Norwich and Sheffield suggested a participation rate of around 24% in those eligible for study entry. This participation rate is likely to be lower than that of a full scale study as publicity was limited and no reminder letters were sent. However, based on this rate, an estimated 50 350 women will need to be invited to join the study in order to achieve a total sample size of 11 580 for randomisation.

3.6 Recruitment

Recruitment will take place through primary care. Primary care practices will be recruited to the study after supplying written information and a visit by one of the local research team to explain the study and what participation would entail.

Subjects meeting the inclusion criteria of being female and aged between 70 and 85 years will be identified by participating GP practices (or by PCT information support services on their behalf). GPs will then be asked to screen out those meeting the exclusion criteria and letters of invitation, signed by GPs, with information leaflets will be mailed to those remaining. Identifiable details will remain within the NHS until written consent has been obtained from participants. There will be an option to decline to participate but to return some demographic and fracture history data, plus a reason for declining, in order to compare with participating subjects. Further, at this stage, potential subjects will be informed of the possibility of being approached to take part in other related studies (e.g. the qualitative studies outlined below). Those agreeing to participate in the SCOOP trial will be asked to indicate (by ticking a box on the consent form) if they would prefer not to be approached about these additional studies.

Reminder letters will be sent after 18 days if no response is initially received. Those willing to participate and returning valid consent forms will be sent baseline questionnaires (see 4.1 for details) and on receipt of these will be entered into the study and randomly allocated to either intervention or control.

Three rounds of invitation, each with a duration of approximately 8 months from invitation to treatment decision and staggered by 4 months, will be carried out to decrease the intensity of work load in each centre (i.e. recruitment will be spread over a 16 month period). This approach will also allow flexibility in the number of invitations sent out in the second and third phases, depending on earlier take up. Based upon data from the pilot study it is anticipated that a total of 50 350 invitations will be required to achieve the necessary sample size. The main phases of recruitment from invitation through to the first follow-up visit are shown in Figure 2.

3.7 Randomisation

Block randomisation (length 6) stratified by age group (70 to 74 years, 75 to 79 years and 80 to 85 years) and general practice. The incidence of fracture is strongly age related making age stratification sensible. Randomisation will be carried out once relevant data is entered into the database based upon a random number generator. This system was successfully used at both centres in the feasibility study.

3.8 Blinding

Blinding of the study participants is clearly not feasible, nor is it feasible to blind all members of the project team actively involved in the execution of the study. The primary endpoint is objective however and very unlikely to be influenced by study subjects' knowledge of group membership. To safeguard against the small residual risk of biased ascertainment of fractures, those research staff responsible for interrogating hospital systems to ascertain fracture outcome will be blinded to group allocation. In addition the member of the study team responsible for outcome analysis will be kept blind to group allocation. The study will therefore have the defining attributes of a single blind study.

Contamination between study arms is another potential problem. Knowing that a subject is participating in the trial, irrespective of study group, may prompt a GP to consider the subject's risk for osteoporosis more carefully than would otherwise have been the case. A possible approach to counter this would be through the use of a cluster randomised design, i.e. randomisation by practice rather than individuals. However, the approach requires a substantially larger sample size. Calculations based upon the recent Sheffield MRC study indicate that around a 3-fold increase in sample size would be required. In addition arguments have been proffered that a cluster randomised approach is often not an efficient means of avoiding contamination [41]. In order to reduce the possibility of contamination, GPs will not be told the weighting given to the clinical risk factors used to calculate the ten-year risk score, nor will they be shown copies of the risk scoring system.

3.9 Follow-Up

Follow-up will be for a minimum of 5 years post-randomisation (longer for those subjects in the earlier phases of recruitment). However, should further funding be available by the termination of the trial, it is anticipated that those subjects remaining in the study will be contacted to request consent for further follow-up as an epidemiological cohort.

3.10 Loss to Follow-Up

The most likely loss to follow-up will be due to death which will be around 4.2% *per annum.* This loss has been explicitly included in the sample size calculation above. It is unlikely that there will be substantial loss to follow-up from migration as this age group tends to be geographically stable.

Any individuals that are lost to follow-up will be included in the main analysis with time to fracture if this is known to be the case or censored at loss-to-follow-up time otherwise.

4. Data Collection and Analysis

Data collection will occur at invitation, baseline (prior to randomisation), at 6 months post-randomisation, 12 months post-randomisation and annually thereafter for a follow-up period of 5 years. A schedule of data collection is shown in Figure 3 and documentation in Figure 4. The array of outcome measures will be deliberately parsimonious, focusing on the outcomes of key interest only and optimizing response rates.

Study participants will be sent questionnaires by post at follow-up to gather self-report fracture data, quality of life and psychological anxiety data, and medication adherence data as detailed below. Closed response data on the quality of life and psychological anxiety

questionnaires will not be monitored routinely. However, if a participant includes written comments on a questionnaire (or other correspondence) that raise serious concerns about her health (particularly when those comments appear to be directed at the GP or other healthcare provider) the local PI or study co-ordinator will contact the participant to discuss the comments and ask whether she wishes the study centre to contact her GP on her behalf regarding the issue. On rare occasions, it may be necessary for the study centre to refer serious concerns about a participant's wellbeing directly to her GP

Prior to the two year follow-up time point, a subset of eligible participants will be randomised in a nested study. Those in the intervention group of the sub-study will receive a combined pre-notification and newsletter approximately six weeks before the follow-up questionnaire is due. Controls will receive their follow-up questionnaire without a pre-notification mailing. If pre-notification is shown to significantly increase initial response rate, consideration will be given to introducing it as a routine measure prior to the remaining follow-up time points. Please see Appendix 1 for further details. Participants eligible for the final questionnaire mailing (five year time point) will be randomised in an additional nested study. The nested intervention group participants will receive a pen enclosed in their mailing in order to test whether this increases questionnaire response rates. Please see Appendix 2 for further details.

It is planned to enter data onto the database using a secure web-based system. This system will incorporate safeguards that will enable each participating site to access their own trial data and participant identifiers, while allowing sharing of anonymised trial data across participating sites. Data will be archived at the University of East Anglia and, after the primary analyses have been carried out, will be available upon request for secondary analyses.

4.1 Invitation and baseline data collection

At the time of the letter of invitation, potential study subjects will be requested to complete and return a consent form and a demographic questionnaire. Baseline questionnaires will be sent to all subjects returning a valid consent form. These will consist of a fracture risk assessment questionnaire, modified SF-12, the EQ-5D (excluding the visual analogue scale), and State-Trait Anxiety Index.

4.2 Efficacy outcome measures

The following efficacy outcomes will be captured:

Primary outcome:

- All osteoporosis-related fractures (ie. excluding those of hands, feet, nose and skull).

Secondary outcomes:

- All clinical fractures (ie. including hands, feet, nose and skull)
- Hip fractures
- Quality of life measures
- Psychological anxiety
- Mortality

Self reported data will consist of the following:

- Demographic details at invitation
- Fracture risk questionnaire at baseline
- EQ-5D at baseline and follow-up
- SF-12 at baseline and follow-up
- State-Trait Anxiety Index at baseline and follow-up
- Fracture questionnaire at follow-up
- Osteoporosis Medications Questionnaire at follow-up

The primary endpoint (all fractures with the exception of those identified above) will be ascertained by combining a range of data sources. At follow-up time points, study subjects will receive a questionnaire requesting details of any fractures during the previous follow-up period, including site of fracture and hospital attendance. Objective fracture information will be obtained via radiology information systems in hospitals serving the study sites and by matching study participants with hospital event records at yearly intervals. NHS number will be key information in this process and will be obtained at the outset for all randomised subjects. By using multiple sources of fracture reporting and confirmation, it will be possible to achieve near complete capture of events. Experience from the large MRC Hip Fracture Study [42] conducted in Sheffield demonstrates using similar approaches that capture of fractures was 100% for hip fracture and between 97% and 98% for other fractures.

Quality of life will be assessed using the self-completed EQ-5D and SF-12 questionnaires. Psychological anxiety will be assessed using the State-Trait Anxiety Index, again self-completed. Anxiety over screening will also be explored using qualitative methods (see below).

Further data will be collected at the DXA scan visit. Height and weight will be recorded. A variety of standard hip BMD measures (*t*-scores, *z*-score, bone mineral content), plus morphological measures for secondary analyses of predictors of fracture will be captured from the DXA scan. At some centres, where facilities exist, muscle-strength data will be taken again to be used for secondary analyses of predictors of fracture. Study subjects will be notified in advance of what the DXA scan will entail.

Prescription information will be captured directly from GP records, starting approximately 5 months after randomisation (ie. approximately 2 months post-treatment recommendation for high risk subjects). Treatment adherence will be captured at follow-up, where appropriate, using the Osteoporosis Medication Questionnaire developed at UEA from the Moriskey and Case index questionnaires.

Mortality will be ascertained by flagging all randomized subjects via the Office of National Statistics.

4.3 Efficacy data analysis

Cox's proportional hazards model will be used to estimate the ratio in hazard between the two groups for fracture (and mortality) together with a 95% confidence interval. Age and study centre will also be included in the model since randomization will be stratified by these variables. Any baseline disparities will also be included.

The analysis of quality of life data will be by a general linear model with age and study centre as factors, and baseline value as a covariate. Again, any baseline disparities will also be included.

Analyses will be on an intention-to-treat basis. Additionally, a subgroup analysis of those actually screened as intended (including DXA scan where necessary) versus control group will be carried out to assess the efficacy of screening (as opposed to its effectiveness).

The data analysis will be the responsibility of Dr Lee Shepstone.

4.4 Qualitative Data Collection and analysis

Two valuable qualitative studies are considered intrinsic to the clinical trial. The first will provide understanding of the acceptability of the community based screening process to both women and GPs, which will be essential when considering the role of screening in practice. The second will collect information on treatment adherence, a factor important for the success of any screening program. Study subjects will not be invited to take part in either of these studies if, at consent, they indicate that they do not wish to be approached

regarding additional studies. Further, no subject will be asked to take part in more than one qualitative study.

Acceptability of screening

The first qualitative study will look at the acceptability of screening to both women and GPs. The study will explore how women experience different dimensions of the screening process that includes risk assessment, potential DXA scanning, and potential opportunities to discuss the results with a GP and receive preventative treatment. As part of this, the study will explore the psychological reaction to, and possible anxiety created by the screening process. This study will also need investigate GPs' views of the screening process, how they feel about discussing results with women and making decisions about treatment options for women identified as high risk.

This qualitative study will take place in Bristol and Norwich. At each site, a purposeful sample of trial participants will be selected, to include those in the high and low risk groups, from different general practices and socio-economic backgrounds, following a maximum variation sampling strategy. Inclusion of both high and low risk women is important as it will allow exploration of both sides of screening. Twenty women from Bristol and 10 from Norwich will be included. A small number of women from the usual care arm will also be interviewed to explore whether being invited to take part in a trial of screening for osteoporosis has an impact on their views of their risk and provokes any anxiety.

Purposeful sampling will also be used to identify a range of GPs from practices participating in SCOOP, across the two qualitative study sites (Bristol and Norwich). The aim will be to include up to 20 GPs who have experienced the SCOOP intervention, for example by discussing DXA results and treatment options with women identified as at high risk of future osteoporotic fracture. We will aim to include GPs from practices with higher and lower proportions of women who have been identified as at high risk.

Interviews with women will occur shortly after DXA scanning and will be conducted in their homes, if acceptable. The interviews with GPs will take place at the surgery, or over the telephone, at their preference. Topic guides will be used to ensure the primary issues are covered in each set of interviews, whilst allowing flexibility for new issues to emerge. Interviews will be recorded using a digital voice recorder, transcribed and anonymised.

Data collection and analysis for each group of participants (women and GPs) will run in parallel. Within each group of participants, preliminary analysis of data from earlier interviews will shape the topics covered in later interviews. The process of data analysis for both datasets will be broadly similar but the two datasets will be dealt with separately, at least in the first instance. The software 'ATLASti' will be used to aid the coding, management and analysis of the data.

Transcripts for the women or the GPs will be studied in detail, beginning with a line-by-line coding of the data, from which an initial coding framework will be developed. This coding scheme will be added to or refined and coded material regrouped as new data are collected. Codes will gradually be built into broader categories and themes. Analysis will draw upon the constant comparative method in which elements of data are continually compared to generate core categories and themes, and earlier analysis shapes later data collection in an iterative process. The data will be scrutinised for confirming and disconfirming views within themes, attention being given to 'deviant' (minority) as well as majority views. Interpretive summaries of the key themes will be produced, with illustrative quotes of the full range of views expressed by participants.

At a later stage, the datasets from the women and the GPs will be compared for common and divergent perspectives regarding key issues, such as their experiences of discussing the screening results and treatment options within a consultation.

The qualitative research associate will meet regularly with the academic lead for the qualitative study (Alison Heawood) to discuss the developing coding framework. The research team for the qualitative study will meet regularly to discuss progress and analysis, and agree emerging themes.

*Adherence to treatment (This sub-study to be known as 'ATOM' – **A**dherence **T**o **O**steoporosis **M**edicines)*

A second qualitative study will be conducted seeking to ascertain the perceived factors that influence older women to adhere to prescribed medication to reduce fracture risk. Potential participants will be purposively sampled from participating high-risk subjects at the Norwich study site, focussing on those patients where initial follow-up data suggest they are (i) not using medication as planned, (ii) those prescribed an alternative treatment after a period on bisphosphonates, or (iii) adherent.

At 6 months post-randomisation, approximately 150 participants will be sent information about the study by post and invited to take part with the aim of recruiting 50 subjects. This mailing will contain a consent form, plus a baseline questionnaire to assess cognitive / emotional factors relevant to medication adherence. Women who return a completed consent form and baseline questionnaire will be contacted by phone to arrange a home visit to conduct an interview about issues related to adherence. An alternative venue for the interview (eg. the Clinical Research and Trials Unit at UEA) will be offered if participants prefer not to be visited at home.

These interviews will aim to cover topics such as understanding of osteoporosis, purpose of medication, current medication usage and any difficulties, main motivators (e.g. risk perception) and detractors for adherence (e.g. lack of immediate evidence of benefit). Relationships with health professionals and views on dosing regimens and formulations and other relevant views including "medicalisation" of later life will be explored. Participants will be asked if they agree to be followed up in approximately 2 years time.

At 2 years follow-up participants will be contacted and a second home-based interview arranged if they are willing to take part. These interviews will cover longer term adherence and factors affecting persistence with treatment.

4.5 Economic Analysis

The determination of cost-effectiveness of the intervention is of central importance. An appropriately designed osteoporosis screening programme might reduce costs of fracture but at the same time it will incur additional costs of detection and treatment.

The analysis will be undertaken from a payer's perspective with a focus upon the direct costs to the NHS, since the majority of costs of fractures fall on the health care system. The collected direct cost data will be as realistic as possible, reflecting current practice. For the screening arm this will include information regarding visits to the general practitioner, DXA scans, subsequent treatment, fractures and other hospital and health service use. Similar data will be collected for patients who are randomised to the control arm. Subsequent data collected at follow-up will include on-going treatment and visits to the GP, hospital and other health services. The valuation of these items will be by reference to standard national price tariffs, unless more accurate costings are available locally. Following accepted economic practice in the public sector, costs and benefits that occur beyond the first year of screening will be discounted using a social discount rate to derive their present value (PV). A sensitivity analysis will be conducted to determine the impact of various discount rates and cost assumptions on the cost-effectiveness ratio.

Since fracture can reduce the quality as well as quantity of life, a cost-utility analysis will also be performed. This involves estimating the cost associated with any between – group difference in the mean number of Quality-Adjusted Life-Years (QALYs) experienced per patient. The EQ-5D will be used to derive QALYs in combination with survival data. This global utility measure will be used for our primary cost-utility analysis. In addition, we will

also use the SF12 data via the SF-6D algorithm to calculate utility values as a sensitivity analysis to our main EQ-5D based cost utility analysis.

5. Trial Management

5.1 Sponsorship

The University of East Anglia will act as sponsor for the main SCOOP study.

Susan Steel
Research & Business Services,
University of East Anglia, Norwich,
NR4 7TJ

The University of East Anglia and NHS Norfolk (primary care trust) will act as co-sponsors for the ATOM sub-study

Dr Tracy Shalom, Research and Development Manager
NHS Norfolk, Broadland Business Park
Thorpe St Andrew, Norwich, NR7 OWG

5.2 Funding

Research funding has been secured for the main SCOOP study from the Medical Research Council and from the Arthritis Research Campaign. The study has also been endorsed by the National Osteoporosis Society, without financial commitment.

There are cost implications for the NHS from several sources, including the cost of treatment, GPs' time, DXA scans and patient transport. Agreement has been secured from the Department of Health that these costs will be covered from Subvention funding (for treatment costs and GP consultations) and Service Support costs (for identification of eligible subjects by GPs, DXAs and patient transport). From 2008/09 service support costs will be met via the UKCRN Clinical Research Network Portfolio. The cost of identifying eligible subjects in the first phase of participant recruitment during 2007/08 will be met through transitional funding arrangements.

Research funding has been secured for the ATOM sub-study from the NIHR Research for Patient Benefit Programme (from 01.01.09).

5.3 Trial Steering Committee

The following have been confirmed by the MRC as Trial Steering Committee members

Elaine Hay	Professor of Community Rheumatology (Independent member & Chair)
Caroline Dore	**arc** representative
John Kanis	WHO Collaborating Centre for Metabolic Bone Diseases (Observer)
Richard Keen	Consultant Rheumatologist (Independent member)
Elizabeth Lenaghan	Trial manager
Eugene McCloskey	Lead clinician & Sheffield Principal Investigator
Mark Pitman	MRC representative
Claire Bowring	National Osteoporosis Society (Observer)
David Scott	Professor of Clinical Rheumatology (Independent member)
Lee Shepstone	Chief investigator
Martin Underwood	Professor of general practice & primary care (Independent member)

This committee will meet initially on a 6-monthly basis and then annually once recruitment has finished.

5.4 Data Monitoring Committee

Vern Farewell	*Chair*
Marwan Bukhari	*Independent clinician*
Dipak Roy	*Independent clinician*

5.5 Recruiting Centres

Seven centres (Norwich, Sheffield, Southampton, York, Birmingham, Manchester and Bristol) will be recruiting to the trial. Each centre will utilise one or more primary care trusts for recruitment.

5.6 Day to day management of the trial

Co-ordination between sites will be the responsibility of the chief investigator (Lee Shepstone) and the trial manager (Elizabeth Lenaghan). The will involve travel to study sites by the latter on a regular basis. A research associate and a clerical post will carry out the day to day activities involved in running the trial at each site. In Norwich these duties will be undertaken by Jeanette Blacklock (local trial co-ordinator) and Veronica Bion (project administrator).

A local trial management group will be formed at each site and will hold meetings on a regular basis.

5.7 Responsibilities of the applicants

Lee Shepstone will act as the Chief Investigator with overall responsibility for the trial and will also act as the trial statistician and the Principal Investigator for the Norwich site. There will be a Principal Investigator responsible for the local running of the trial at each of the other six sites (Eugene McCloskey, Cyrus Cooper, David Torgerson, Tim Peters & Alison Heawood (Co-PIs), Terence O'Neill and Neil Gittoes) together with methodological input to the trial. In addition, Eugene McCloskey will be the lead clinician for the study. John Kanis will provide methodological advice regarding the screening procedure. Alison Heawood will provide the academic lead for the qualitative aspect of the study investigating participants' reactions to screening. Amanda Howe will be the lead primary care academic and lead the qualitative adherence study in conjunction with Charlotte Salter. Ric Fordham will be responsible for leading the economic evaluation. Tarnya Marshall will be the lead rheumatologist for the Norwich site. Richard Holland will provide further clinical trials advice and be the lead public health specialist.

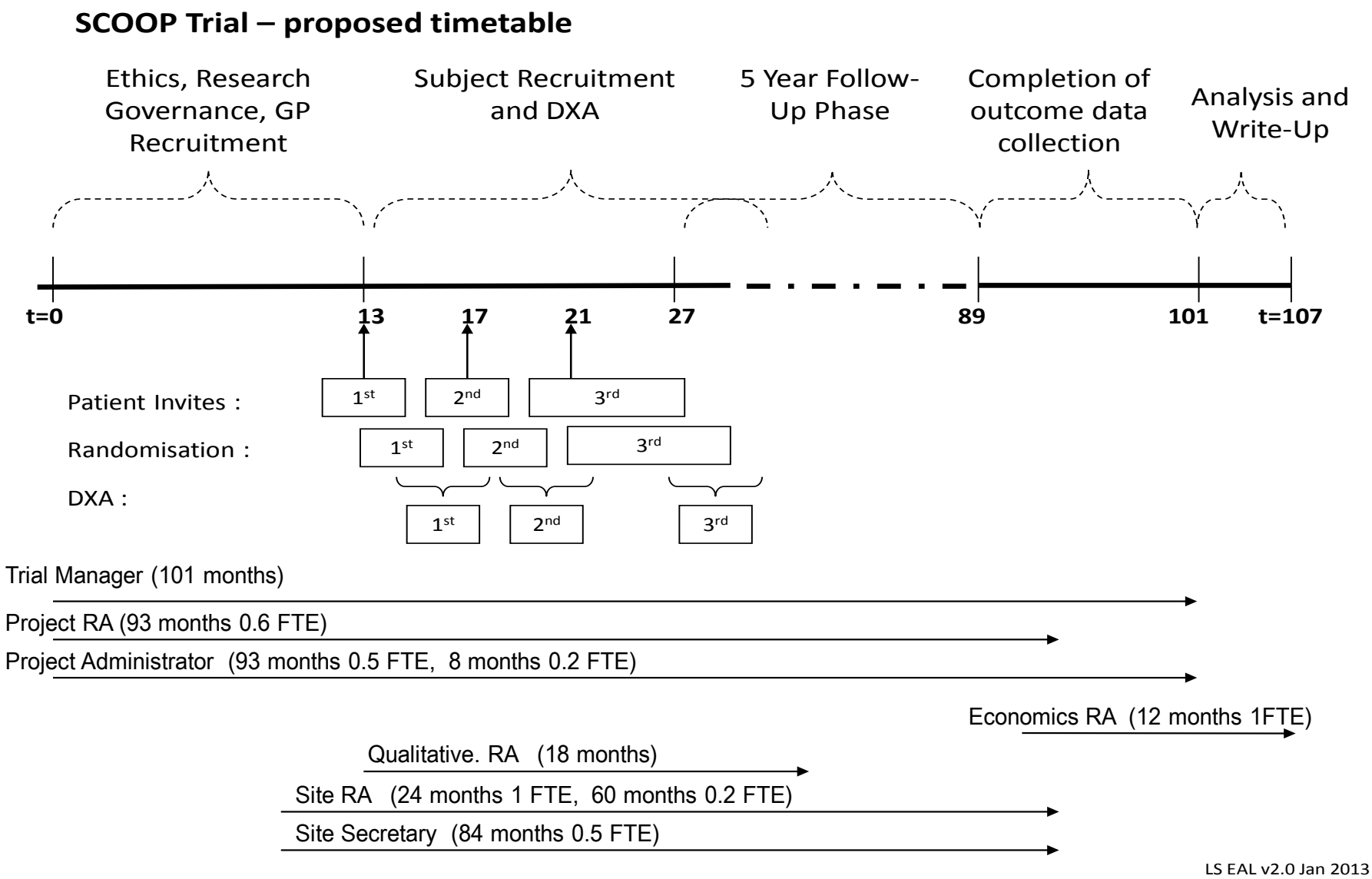
Randomisation will be administered locally by the site research associates using a secure web-based central randomisation procedure. Data will be entered locally using manual and automatic data entry (as used in the feasibility study) and added to the central database housed at Norwich, again using a web-based system.

References

1. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement 2000 March 27-29;17: 1–45.
2. Kanis JA, Glüer CC. An update on the diagnosis and assessment of osteoporosis with densitometry. *Osteoporos Int* 2000;11:192-202.
3. World Health Organisation. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO Technical Report Series, Geneva 1994.
4. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis Int* 2006; 17(12):1726-1733
5. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. *Arch Inter Med* 1991;151:2026-2032
6. Royal College of Physicians. Clinical guidelines for the prevention and treatment of osteoporosis. London: RCP, 1999.
7. Eddy DM, Johnston CC Jr., Cummings SR *et al*. Osteoporosis: Review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. Status report. *Osteoporos Int* 1998;8(S4): S1-S82
8. Cummings SR, Melton III LJ. Osteoporosis I: Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002; 359:1761-1767
9. Torgerson DJ, Iglesias CP, Reid D. The economics of fracture prevention. In The Effective Management of Osteoporosis. Eds Barlow DH, Francis RM, Miles A. Aesculapius Medical Press. London: 2001.
10. Chapuy MC, Arlot ME, Duboeuf F, *et al*. Vitamin D3 and calcium to prevent hip fractures in elderly women. *N Eng J Med* 1992; 327:1637-1642
11. Dawson-Hughes B, Harris SS, Krall EA, *et al*. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Eng J Med* 1997;337: 670-676
12. Roux C. Reginster J-Y. Fechtenbaum J. Kolta S. Sawicki A. Tulassay Z. Luisetto G. Padrino J-M. Doyle D. Prince R. Fardellone P. Sorensen OH. Meunier PJ. Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. *J Bone Miner Res* 2006;21:536-542.
13. Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative RCT. *JAMA* 2002;288:321–33.
14. McClung M, Geusens P, Miller P, *et al* Effect of Risedronate on the risk of hip fracture in elderly women. *N Engl J Med* 2001; 344:333-40.
15. Hodsman AB, Hanley DA, Josse R. Do bisphosphonates reduce the risk of osteoporotic fractures? An evaluation of the evidence to date. *CMAJ* 2002; 166:1426-30.
16. Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M. Treatment of established osteoporosis: a systematic review and cost-utility analysis. *Health Technol Assess 2002*; 6(29):1-146
17. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996; 312:1254-1259
18. SCE Schuit, M van der Klift, AEA Weel, *et al*. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. *Bone* 2004;34:195-202
19. SA Wainwright, LM Marshall, KE Ensrud, *et al*. Hip fracture in women without osteoporosis. *J Clin Endocrinol Metab* 2005; 90:2787-93.
20. Kanis JA, Borgstrom F, De Laet C *et al*. Assessment of fracture risk. *Osteoporosis Int* 2005; 16(6):581-589.
21. McGrother CW, Donaldson MMK, Clayton D, Abrams KR, Clarke M. Evaluation of a hip fracture risk score for assessing elderly women: The Melton osteoporotic fracture study. *Osteoporos Int* 2002; 13:89-96
22. Black DM, Steinbuch M, Palermo L, *et al*. An assessment tool for predicting fracture risk in postmenopausal women. *Osteoporos Int* 2001; 12:519-528.
23. van Staa TP, Leufkens HGM, Cooper C. Utility of medical and drug history in fracture risk prediction among men and women. *Bone* 2002; 31:508-514.
24. Kanis JA, Oden A, Johnell O *et al*. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007 Feb 24; [Epub ahead of print]
25. Oden A, Dawson A, Dere W, *et al*. Lifetime risk of hip fracture is underestimated. *Osteoporos Int* 1998;8:599-603
26. Johansson H, Oden A, Johnell O, *et al* Optimisation of BMD measurements to identify high risk groups for treatment – a test analysis. *J Bone Miner Res* 2004;19:906-913.

27. Kanis JA, Johnell O, Oden A*, et al*. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. *Bone* 2000; 27:585-590
28. Kanis JA, Johnell O, Black DM, Downs RW, Jr., Sarkar S, Fuerst T, Secrest RJ, Pavo I. Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. *Bone* 2003;33:293-300.
29. Kanis JA, Barton IP, Johnell O. Risedronate decreases fracture risk in patients selected solely on the basis of prior vertebral fracture. *Osteoporos Int* 2005;16(5):475-82.
30. Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of-1.6 to -2.5 at the femoral neck: the Fracture Intervention Trial. *Mayo Clin Proc* 2005;80(3):343-9.
31. Wilson JMG, Jungner G. Principles and Practices of Screening for Disease. Geneva: World Health Organisation, 1968.
32. The clinical effectiveness and cost effectiveness of technologies for the secondary prevention of osteoporotic fractures in postmenopausal women. National Institute for Health and Clinical Excellence, Technology Assessment 87. January 2005.
33. La Croix AZ, Buist DSM, Brenneman SK, et al. Evaluation of three population-based strategies for fracture prevention: results of the OPRA trial. *J Bone Miner Res* 2002;17:260.
34. Torgerson DJ, Donaldson C, Russell IT, *et al*. Hormone replacement therapy: compliance and cost after screening for osteoporosis. *Eur J Obstet Gynaecol* 1995;59:57-60
35. Barr RJ, Stewart A, Torgerson DJ, et al. Screening elderly women for risk of future fractures – participation rates and impact on incidence of falls and fractures. *Calcif Tissue Int* 2005;76:243-238
36. Rimes KA, Salkovskis PM, Shipman AJ. Psyhological and behavioural effects of bone density screening for osteoporosis. *Psychology and Health* 1999;14:585-608
37. Reventlow SD, Hvas L, Malterud K. Making the invisible body visible. Bone scans, osteoporosis and women's bodily experiences. *Soc Sci Med* 2006;62:2720-2731
38. Kanis JA, Borgstrom F, Zethraeus N, et al. Intervention thresholds for osteoporosis in the UK. *Bone* 2005;36:22-32
39. Lakatos E, Lan K. A comparison of sample size methods for the logrank statistic. *Stats Med* 1992; 11:179-191
40. van Staa, TP, Dennison, EM, Leufkens, HGM, *et al*. Epidemiology of fractures in England and Wales. *Bone* 29:517–522; 2001.
41. Torgerson DJ Contamination in trials: is cluster randomization the answer? *BMJ* 2001; 322:355-357
42. McCloskey E, Selby P, Davies M*, et al*. Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004;19(5):728-36.

Figure 1: Study Timeline



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Figure 2 : Main events within recruitment phases

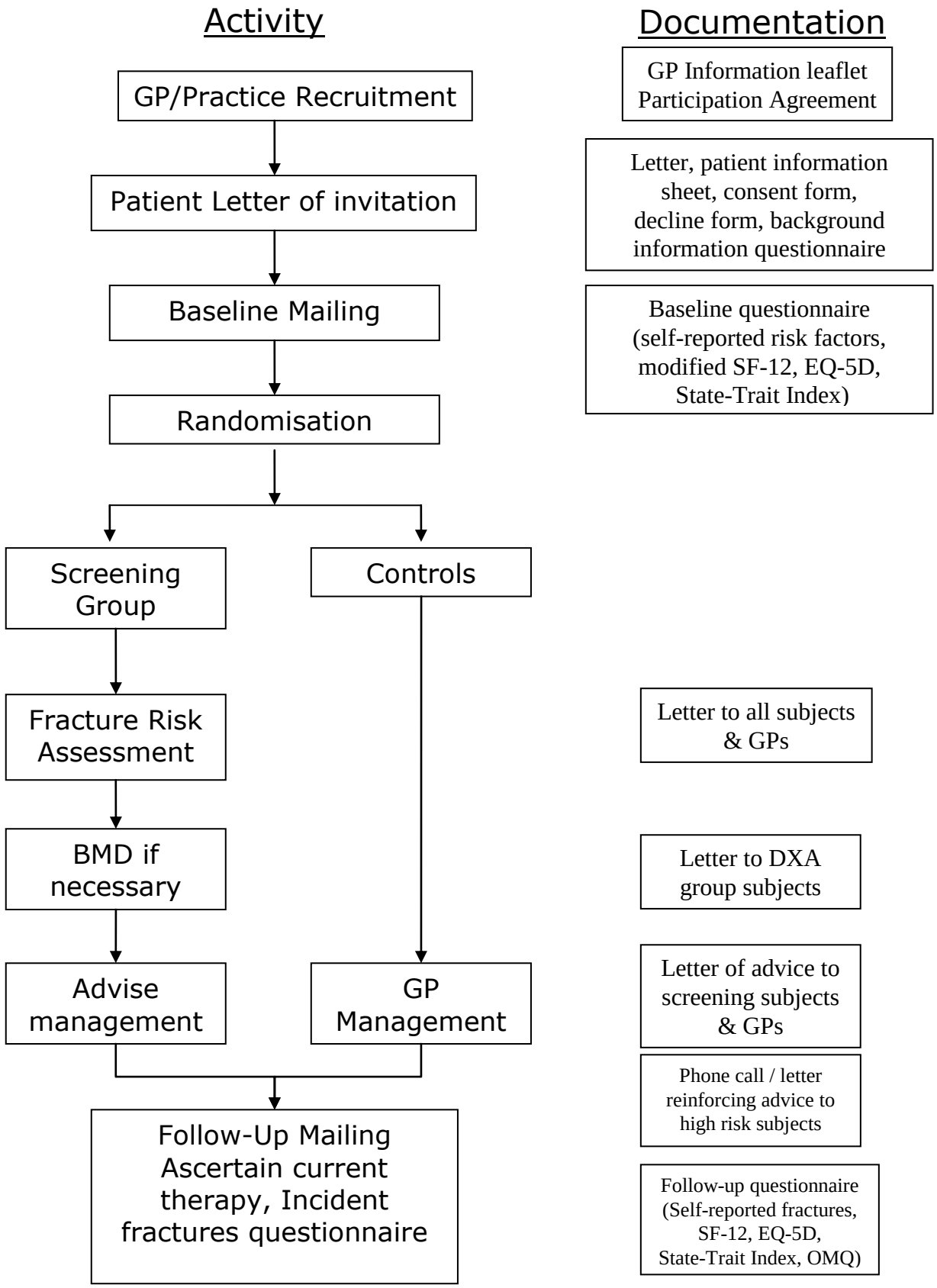
Time†	Activity	Study Subjects
-4	Invitation mailing for trial	All eligible
-3½	Reminder Letter	Non-responders after 18 days
-2	Baseline mailing	All consenting
0	Randomisation	All consenting with baseline data
+½	GP/Subject Letter advising study group and risk level	Control group & Low risk group
+1 to +4	DXA Scans	High risk group
+1 to +4	GP/Subject Letter advising treatment group	High risk group
+1½ to +4½	Invitation mailing for anxiety qualitative study	High risk group available for additional studies
+5	Start medication data collection	All randomised
+6	Medication phone call / mailing	High risk group
+6	Follow-Up Mailing	All randomised
+6	Invitation mailing for adherence qualitative study	High risk group available for additional studies

† Approximate time in months relative to randomisation

Figure 3 : Data Collection Schedule

	Invitation	Baseline	DXA Scan Visit	6 Month Follow-Up	Annual Follow-Up
Consent/Decline form	✓				
Demographic questionnaire	✓				
Risk factor questionnaire		✓			
SF-12 questionnaire		✓		✓	✓
EQ-5D questionnaire		✓		✓	✓
State-Trait Anxiety Index		✓		✓	✓
Hip BMD for DXA group			✓		
Height and Weight			✓		
OM questionnaire				✓	✓
Fracture questionnaire				✓	✓
Objective incident fracture quest via HES data etc.					✓

Figure 4 : Summary of study activities and documentation



APPENDIX 1 – Protocol addendum (added 01/10/09)

SCOOP sub-study: A nested randomised controlled trial of combined pre-contact and newsletter for increasing questionnaire response rates in SCOOP trial participants.

1. Background

Postal questionnaires are widely used in health research and poor response rates can introduce non-response bias and reduce statistical power [1, 2]. Studies in the elderly population have been shown to achieve a response rate of 60% or less [3, 4]. Therefore, methods which can be implemented to improve response rates are highly relevant to health research. There have been two large reviews [5, 6] of improving response rates, both of these have identified pre-contact as a method for increasing response rates to questionnaires. Methods of pre-contact in previous studies have included contact by either a letter, postcard or telephone call to the participant. A Cochrane review [5] carried out a meta-analysis of 39 pre-contact studies, and found if participants were pre-notified the odds of response were increased by half. McColl et al. [6] examined pre-contact and mode of contact in a recent HTA report and similarly found strong evidence of the benefit of pre-contact. Although there have been a number of studies examining the benefit of pre-contact very few of these are specifically in health and there are currently no studies examining response rate and participant newsletter.

2. Objective & method

Currently, in the SCOOP Study there is no contact between the study centre and the participant during the period between questionnaire follow-ups. The purpose of this sub-study is to randomly allocate participants to receive a combined pre-notification and participant newsletter to evaluate if this will increase response rates to the SCOOP 2 year follow-up questionnaire (due to start in 2010). By providing participants with a newsletter the SCOOP Study team will be able to remind participants they are participating in the study, why their participation is important, and that they will soon be receiving a questionnaire. It also provides an opportunity to inform participants about the progress of the study across the country and locally.

Participants in the study will be randomly assigned to either receive a newsletter or no newsletter. We would aim to send participants the newsletter approximately 6 weeks before their 2 year follow-up questionnaire is due. We propose to include participants who were randomised in 2008; this method allows us to capture the majority of participants and allows sufficient time for analysis and a decision regarding whether participants are routinely sent a newsletter prior to their questionnaire if the method is shown to improve response rates. We anticipate our sample size will be approximately 1,600 participants. As this is a 'sub-study' nested in a larger RCT of osteoporosis screening, our sample size

has been constrained by the number of participants recruited to the study. However, we anticipate sending out approximately 1,600 questionnaires which would give us approximately 60% power to detect an absolute difference of 5% (2p = 0.05) between the two groups, using a baseline of 70%.

3. Outcome

If the combined pre-notification and newsletter intervention significantly increases the initial response rate at the 2 year follow-up time point, consideration will be given to introducing it as a routine measure prior to the remaining questionnaire follow-up time points.

4. References

1. Smeeth L, Fletcher AE. Improving the response rates to questionnaires. BMJ. 2002;324:1168-9.
2. Taylor KSM, Counsell CE, Harris CE, Gordon JC, Fonseca SCC, Lee AJ. In a randomized study of envelope and ink colour, coloured ink was found to increase the response rate to a postal questionnaire. J Clin Epidemio. 2006;59:1326-30.
3. Hardie JA, Bakke PS, Mørkve O. Non-response bias in a postal questionnaire survey on respiratory health in the old and very old. Scand J Public Health. 2003;31:411-7.
4. Paganini-Hill A, Hsu G, Chao A, Ross RK. Comparison of early and late respondents to a postal health survey questionnaire. Epidemiology. 1993;4:375-9.
5. Edwards PJ, Roberts IG, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I, et al. Methods to increase response rates to postal questionnaires. Cochrane Database of Syst Rev: Cochrane Database of Syst Rev; 2007.
6. McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, et al. Design and use of questionnaires: A review of best practice applicable to surveys of health service staff and patients. Health Technology Assessment. 2001;5(31).

APPENDIX 2 – Protocol addendum (added 31/01/13)

A randomised controlled trial of including a pen with a follow-up questionnaire for increasing questionnaire response rates in older women.

1. Background

Postal questionnaires are a useful tool in health research and are frequently employed. If there is a poor response to these questionnaires a non-response bias can be introduced and statistical power is reduced, therefore leading to potentially poor quality results from which conclusions cannot be drawn [1, 2].

Previous studies within an elderly population have yielded a response rate of 60% or less [3] so strategies to increase response rate are important. These studies have also shown that there are differences between the characteristics and outcomes of non-responders and responders [4-7] thus methods to increase response rates are both pertinent and necessary.

One such method to increase response rate that has been identified is to include a pen with the questionnaire. There are mixed results regarding the effectiveness of such an intervention. White et al [8] found that including a study-logo pen or pencil to non-responders in a second mailing was a cost effective way of increasing response rates. Similarly Sharp et al [9] have shown that enclosing a pen with questionnaires significantly increases the response rate from 61.5-68.5% (P=0.002) in their patient population.

Conversely studies by Clark et al and Stange et al [10, 11] have shown no significant difference. However these studies were performed on medical consultants and 'recent college graduates'. Similarly a systematic review [12] assessing different methods to increase response rate to questionnaires found no significant difference when a pen was included with the questionnaire. Again, this trial targeted clinicians and not a patient population.

When reviewing the literature it can be seen that there are few large scale studies which have been carried out within a patient population. More trials are necessary to assess whether including a pen with questionnaires affects the response rate and thus attrition in a healthcare trial.

2. Objectives

The primary aim of this trial is to compare the effect of receiving a pen with the study logo with the standard first follow-up questionnaire sent on response rates to postal questionnaires.

The secondary aims of this study are to assess whether receiving a pen with the study logo has an effect on: the number of reminders sent, the completeness of the primary outcome and the time to return the questionnaire to the study centre.

3. Trial Design

3.1 Increasing response rates

The trial design is a two-armed pragmatic randomised controlled trial. All women that remain consented to receive a hard copy of the SCOOP 5 year follow-up questionnaire in 2013 will be included in this sub-study. A computer randomisation package will be used to randomise all eligible participants to either receive a pen with the SCOOP study logo on with their 60-month questionnaire or receive their 60-month questionnaire alone. Study logo pens will be included with the original 60 month follow-up questionnaire; where a reminder questionnaire is necessary a study logo pen will not be included with this reminder mailing. We anticipate our sample size will be approximately 8000 participants. As this is a 'sub-study' nested in a larger RCT of osteoporosis screening, the sample size has been constrained by the number of participants recruited to the study and have consented to receive follow-up by paper questionnaire. However, we anticipate sending out approximately 4000 pens which would give us approximately 60% power to detect an absolute difference of 5% (2p = 0.05) between the two groups, using a baseline of 90%.

4. Statistics

All analyses will be conducted in Stata using two-sided significance testing at the 5% significance level on an intention to treat basis.

The primary outcome is the overall questionnaire response rate (number of patients who returned the follow up questionnaire divided by the number that did not for the intervention and control groups).

The secondary outcomes are: number of reminders sent (number of participants requiring a reminder mailing divided by the number of participants sent a questionnaire), completeness of the primary outcome (number of participants with a complete primary outcome divided by the number of patients returning a questionnaire) and time to response (the time to return the questionnaire to the study centre).

Univariate odds ratios (ORs) will be calculated for each response rate and the log rank test shall be used to compare the time to response between the intervention and control groups.

5. Ethics

Ethical approval will be necessary for this sub-study as participants randomised to receiving a SCOOP study logo pen will be receiving an additional item with their questionnaire.

6. References

1. Edwards, P., et al., *Increasing response rates to postal questionnaires: systematic review.* Bmj, 2002. **324**(7347): p. 1183.
2. Smeeth, L. and A.E. Fletcher, *Improving the response rates to questionnaires.* Bmj, 2002. **324**(7347): p. 1168-1169.
3. Hardie, J.A., P.S. Bakke, and O. Mørkve, *Non-response bias in a postal questionnaire survey on respiratory health in the old and very old.* Scandinavian journal of public health, 2003. **31**(6): p. 411-417.
4. Cull, W.L., et al., *Response rates and response bias for 50 surveys of pediatricians.* Health services research, 2005. **40**(1): p. 213-226.
5. Partin, M.R., et al., *The impact of survey nonresponse bias on conclusions drawn from a mammography intervention trial.* Journal of clinical epidemiology, 2003. **56**(9): p. 867-873.
6. Solberg, L.I., et al., *Nonresponse bias: does it affect measurement of clinician behavior?* Medical care, 2002. **40**(4): p. 347-352.
7. Van Loon, A.J.M., et al., *Survey non-response in the Netherlands: effects on prevalence estimates and associations.* Annals of epidemiology, 2003. **13**(2): p. 105-110.
8. White, E., P.A. Carney, and A.S. Kolar, *Increasing response to mailed questionnaires by including a pencil/pen.* American journal of epidemiology, 2005. **162**(3): p. 261-266.
9. Sharp, L., et al., *Enclosing a pen with a postal questionnaire can significantly increase the response rate.* Journal of clinical epidemiology, 2006. **59**(7): p. 747-754.
10. Clark, T., K. Khan, and J. Gupta, *Provision of pen along with questionnaire does not increase the response rate to a postal survey: a randomised controlled trial.* Journal of epidemiology and community health, 2001. **55**(8): p. 595-596.
11. Stange, J.P. and S.J. Zyzanski, *The Effect of a College Pen Incentive on Survey Response Rate Among Recent College Graduates.* Evaluation review, 2011. **35**(1): p. 93-99.
12. VanGeest, J.B., T.P. Johnson, and V.L. Welch, *Methodologies for Improving Response Rates in Surveys of Physicians A Systematic Review.* Evaluation & the Health Professions, 2007. **30**(4): p. 303-321.