Work in progress – comments welcomed (to j.p.raftery@bham.ac.uk)

NOT FOR CITATION

Does secondary prevention in coronary heart disease pay for itself? Issues in the economic analysis of an RCT and four-year follow up.

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ABSTRACT

Study objectives

To explore issues around estimation of net cost per patient, including use of Intention to Treat (ITT) versus exposure analysis, aggregation of cost elements, a disease-specific or all disease focus, and the inclusion or not of the costs of death, based on the results of an RCT of nurse led secondary prevention clinics for coronary heart disease and its four year follow up.

Design

Follow up of a randomised, controlled trial including patient measurements, interviews and routine data sources on resource use and costs and on mortality.

Setting

A stratified, random sample of 19 general practices in north-east Scotland.

Subjects

1,343 patients (673 intervention and 670 control as originally randomised) under 80 years with working diagnosis of coronary heart disease but without terminal illness, dementia and not housebound. Patients were followed up four years later.

Methodology

General practice records were reviewed during practice visits. A postal questionnaire was sent to surviving patients. Data was obtained on trial patients' use of inpatient and outpatient services (and deaths) from ISD Scotland.

Main Results

- **Uptake** (by ITT): At 1 year all components of secondary prevention except smoking had improved in the intervention group. At four years, these improvements were sustained except for exercise, but the control group, most of whom had since attended clinics, had caught up. Longer clinic attendance was associated with better secondary prevention.
- **Health outcomes** (by ITT)**:** These were part of the one-year design. At 4 years, the intervention group had: fewer role limitations attributable to physical problems, fewer coronary events (100 out of 673 (14.9%) compared with 125 out of 670 (18.7%) in the control group (p= 0.062)), and significantly fewer deaths (100 (14.9%) compared with 128 (19.1%) in the control group (p=0.038)).

- **Costs (**By ITT): In each year, there were no significant differences in mean total cost per patient, with the (statistically significant) increased cost of secondary prevention (clinic attendance plus medication) offset by reduced hospital stays for CVD events. These cost results at either one or four years were unaffected by use of different approaches to ITT and by exclusion of the costs of CVD related deaths in hospital.
- **Benefits** (by exposure): longer exposure was associated with improved outcomes (almost all improvements in secondary prevention at 12 months were retained at four years).
- **Cost** (by exposure): mean total cost per patient was lower (but not statistically significantly so) in those with some exposure compared to those with none, and did not vary by duration of exposure.

CONCLUSIONS

Policy: As health outcomes were better in the intervention group and mean total cost per patient no higher, the intervention was 'dominant' in both ITT and exposure analyses. Secondary prevention appears to pay for itself, and within short time periods. Due to their importance, the technical issues around the costing deserve attention.

Context

Between 1994 and 1995 a randomised controlled trial of nurse led clinics for the secondary prevention of coronary heart disease was conducted in north-east Scotland. Randomisation was by individual and the intervention group was invited to attend nurse-led clinics, which sought to promote medical, and lifestyle aspects of secondary prevention. This showed statistically significant improved take up of secondary prevention in the intervention arm (aspirin, blood pressure management, lipid management, and physical activity), but not on smoking. Statistically significant improvements were shown in 6 of the 8 health status measurements and for reduced hospital admissions.

The principal aims of the follow up study was to evaluate at four years:

a) the effects of nurse led secondary prevention clinics for coronary heart disease on the use and uptake of components of secondary prevention,
b) to assess their impact on health and mortality, and
c) the cost implications along with cost effectiveness analysis if and as appropriate.

Research Questions

This paper focuses mainly on the methodological issues in costing:

a) implications of ITT for economic analysis,
b) implications of using exposure analysis as an alternative to ITT,
c) the aggregation of statistically significant cost elements with those that are not,

d) the degree to disease specific or all cause knock on effects should be included,

e) the role of deaths in costs.

METHODOLOGY

Review of General Practice Records

Data was extracted from general practice case notes and computer records at practice visits and entered onto a portable computer on site. Data was collected on drug treatment, blood pressure and lipid management, hospital admissions, cardiovascular events (e.g. myocardial infarction) and procedures (coronary artery bypass grafting and coronary angioplasty) and record of attendance at secondary prevention clinics.

Postal Questionnaire

A questionnaire collected data about exercise and smoking, diet, health status (SF-36), chest pain and anxiety and depression (HAD scale). Data were also collected on use of private health care facilities and use of nursing or residential homes.

Review of National Datasets

Death data (dates and causes of death) and data on hospital admissions were obtained from the Information and Statistics Division, NHS Scotland.

Costing

Costs to primary care of running the CHD clinics during the four years of the study were calculated. The yearly and total attendances at clinics were calculated for each group. It was assumed that each attendance lasted one hour. The costs of clinic materials and training were included at year one. At years two, three and four it was assumed that the only cost incurred in running the clinics was nurse time and this was estimated at £20.00 per hour. Based on an audit of nurse time and interviews with practices, those patients who attended in the first year of the clinics were attributed two visits and patients who attended in any of the subsequent years one visit The costs of the intervention included the costs of cardiac related drugs, based patient interviews and casenotes at three points: baseline, 12 months and 48 months. Cardiovascular drug prescriptions were costed based upon the Scottish Drugs Tariff. The costs of hospital admissions were calculated by assigning the appropriate unit cost per case based on specialty and location and deriving costs per patient and total costs by group.[1]

Outpatient costs were based on the number of attendances multiplied by the relevant hospital unit cost. As data were incomplete on outpatients, missing data was imputed based on the average ratio of outpatient attendances per CVD admission for surviving patients. As the share of total cost per patient accounted for by

[1] Scottish NHS Costing Returns, 1998/9.

outpatients was small, the imputation of these missing values made very little difference to total cost per patient.

Private hospital costs were based on the number of cardiac procedures multiplied by the relevant local NHS unit cost. Again as these costs accounted for a very small % of total cost per patient, the effects of this assumption were minimal.

While the perspective aimed to be a close to societal as possible by including private hospital costs, the predominance of NHS costs means that the NHS perspective is almost identical.

Statistical Analysis of health benefits

Binary outcomes were analysed using logistic regression and continuous variables using analysis of covariance. For total mortality and coronary event data Kaplan Meier survival curves were constructed and analysed using the log rank test. A supplementary analysis using Cox regression adjusted for age, practice and sex. The main analysis of outcomes was by intention to treat (ITT).

While ITT is appropriate for the period in which the trial took place (year 1 below), its application to the follow up of patients who 'crossed over' from the control to the intervention arm means that any differences in outcomes are minimised. Those GP practices that continued to run clinics after the trial extended the service to those patients with CHD who had been randomised to the control group. The result was that only 45% of patients in the control group had had no exposure to the secondary prevention clinics by the end of the four-year follow up period (compared to 13% in the intervention group).

The implications of ITT for costing, which have received little attention in the literature, were explored in the cost analysis.

HEALTH BENEFIT RESULTS

ITT analysis

In the intervention group, there were significant improvements in all components of secondary prevention (aspirin, blood pressure, lipids, exercise, and diet) except smoking at one year. At four years, these improvements were sustained except for exercise. Differences with the control group were significant for all components except smoking at one year, but by four years, the performance of the control group had improved and differences were no longer significant.

Total Mortality

At follow up there were 100 (14.9%) deaths in the intervention group out of 673 compared with 128 (19.1%) out of 670 in the control group. Survival analysis was performed to account for 16 individuals who left Scotland by censoring at time of loss to follow up. Cumulative death rates were 14.5% for the intervention group and 18.9% for control (p=0.038), and the relative risk for total mortality was 0.78 (95% confidence intervals 0.61 to 0.99). Adjusting for age, practice size, sex and baseline secondary prevention, the adjusted hazard ratio was 0.73 (95% confidence intervals 0.55 to 0.98, p=0.034).

Coronary Death or Non Fatal Myocardial Infarction

At follow up the number of coronary deaths or non fatal myocardial infarctions in the intervention group was 100 out of 673 (14.9%) compared with 125 out of 670 (18.7%) in the control group. Using survival analysis cumulative event rates were 14.2% for intervention and 18.2% for control (p=0.052) and the relative risk for coronary events was 0.80 (95% confidence intervals 0.63 to 1.01). Adjusting for age, practice size, sex and baseline secondary prevention, the adjusted hazard ratio was 0.74 (95% confidence intervals 0.55 to 1.00, p=0.047).

Exposure analysis

In this supplementary analysis, longer attendance at clinics was associated with improved secondary prevention for aspirin, blood pressure and lipid management, and improved exercise, although improvements in exercise were no longer significant after adjusting for other variables. Diet and smoking status did not vary with length of attendance at clinics. These differences could have been exaggerated by the 'healthy attender' effect, although little association was found in a further analysis between attendance at clinics and healthy lifestyles.

Cost analysis

Of primary interest was the degree to which the intervention's increased cost per patient (clinic attendance twice per annum in year one and annually thereafter, plus the cost of changed medications) were offset by the reduced hospital costs due to fewer cardiac deaths and events. If there was no significant increase in net mean total cost per patient, then cost effectiveness analysis would be unnecessary. Given improved benefits and no increase in costs, secondary prevention would be dominant over conventional care.

This approach was prompted by two factors. First, the study did not incorporate outcome measures (coronary events, angina and depression scores, SF36) appropriate to cost effectiveness analysis. Second, the original report of the one-year trial results [2] noted a reduction in hospital admissions, which prompted interest in exploring the extent of these cost offsets.

Two broad approaches to costing were taken:

A) ITT and B) Exposure to secondary prevention.

A) ITT analysis

ITT, which compares two groups based on their original randomisation, follows the analysis by our co-authors of health outcomes at four years[3].

Three forms of ITT cost analysis were carried out:

i) by intention to treat, with all participants originally randomised to each group as the denominator for that group for each year when calculating cost per participant.

ii) by intention to treat, but using the number of participants alive at the mid-point of each year as the denominator when calculating cost per participant

iii) as ii) but removing the costs of those patients who died from cerebrovascular disease (CVD).

B) Exposure analysis

The main limitation of ITT in the follow up study had to do with patients 'crossing arms'. Control patients in practices which maintained clinics were able to use the secondary prevention service, and so had exposure. Some practices discontinued clinics (and some re-started) so that some intervention patients had their exposure withdrawn for varying periods. And some patient's exposure was terminated, mainly by death, serious illness or in a small number by moving away from Scotland.

In the exposure analysis, five groups were compared over time: those with zero, one, two, three and more than 3 years exposure. The analysis was limited to patients who were alive at the end of the follow up, and thus excluded all those who died or left Scotland. Thus the focus is on those live patients with some degree of exposure to secondary prevention. The analysis of outcomes showed greater health benefits for those with greatest duration of exposure. If this was associated with increased cost per patient, then cost effectiveness analysis might be required.

Analysis methods

The mean difference in cost per patient in each approach was analysed by bootstrapping[4].

[2] Campbell NC, et al Secondary prevention clinics for coronary heart disease: randomized trial of the effect on health, BMJ 1998, 316: 1434-7

[3] Campbell NC et al. Secondary prevention in coronary heart disease. Four year follow up and economic evaluation of a randomized trial in primary care. Dept General Practice, University of Aberdeen. Report to Chief Scientist Office. Scottish Executive. 1999.

[4] Comparisons were made between bootstrapping and T tests, some traces of which remain in the text. More detailed discussion of this issue was omitted on the grounds that the results were as might be expected given the dataset, that is no difference between the two methods in terms of statistical significance.

RESULTS

Follow Up

1,343 patients were recruited to the original study. 673 subjects were randomised to receive the intervention and 670 were randomised to control (figure 1). At follow up 100 members of the intervention group had died and 9 had left Scotland. Case note data was collected on 564 intervention group subjects and 500 (89%) of these returned the study questionnaire. Of 670 control groups subjects, at follow up 128 had died and 7 had left Scotland. Case note data was collected from the remaining 534 patients and 461 (86%) of these returned the study questionnaire.

Mean follow up was at 4.7 years. Intervention and control groups were well matched for age, sex and practice characteristics at baseline and follow up.

Of the 19 original study practices 10 had continued to run clinics after the trial, until follow up. 3 practices had stopped running clinics after the study year and had not resumed. 6 practices had stopped running clinics after the study but following a break had resumed and were running clinics at follow up. See figure A1 for an overview.

Cost Results

A) ITT

A i) strict ITT

Figure 1, 2, and 3 (and Table A.1) shows the mean intervention, NHS inpatient and total cost by arm and years, indicating that:

- mean cost per patient associated with the intervention (cost of secondary clinic attendance plus changed CHD drug prescriptions) was higher in the intervention group in all years after year 1 (baseline) as might be expected and statistically significant (figure 2)
- the intervention group had lower NHS inpatient mean cost for CVD in each year, which offset the increased cost of the intervention although this difference was not statistically significant in any year. (figure 3)
- mean total cost was not significantly different in any year (figure 4).

Figure 1

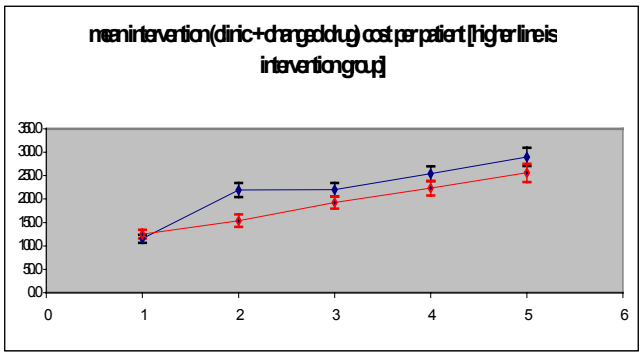


Figure 2

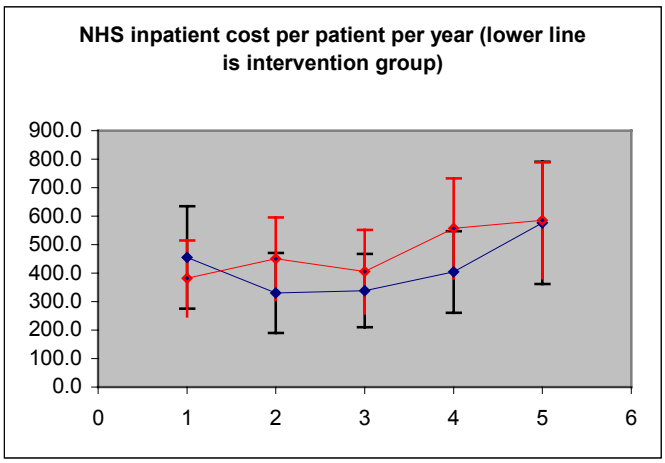
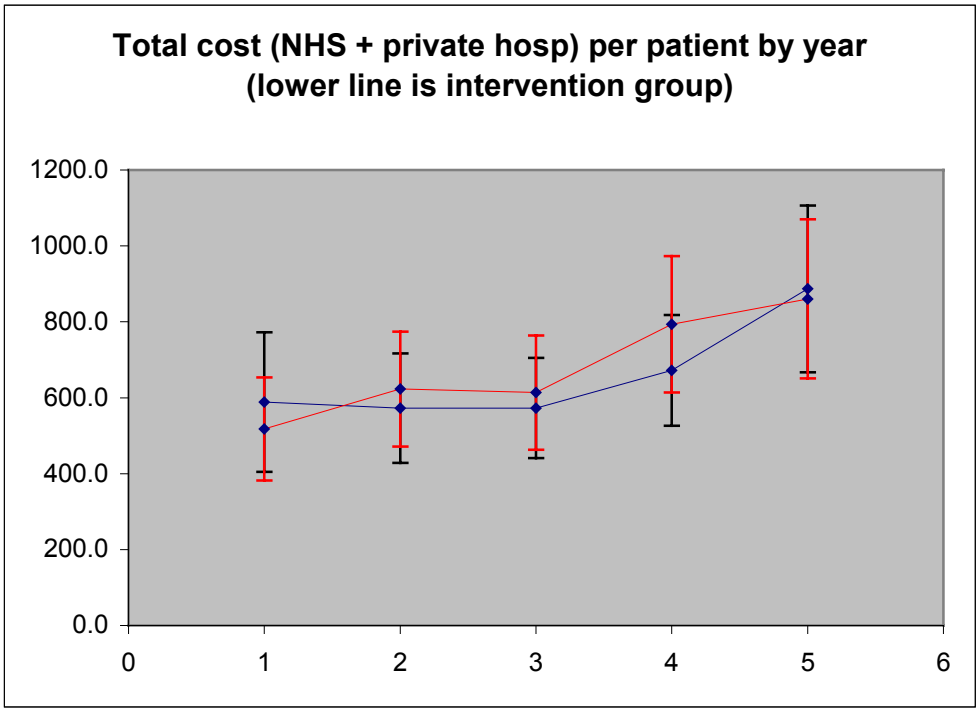


Figure 3



Note to figures: the confidence intervals shown in the 3 figures above were based on t tests rather than bootstrapping (bootstrapping is our preferred analysis). However as shown in Table A3, the use of t tests gives the same results as bootstrapping in terms of statistical significance.

A ii) ITT survivors only

The pattern of costs by arm and year was raised per patient due to reducing the denominator by those who had died (see Table A4).

The cost of the intervention was significantly different between arms in each year, and higher for the intervention group as expected. The cost of NHS inpatient spells was lower for the intervention group in all years but not statistically different.

The mean total cost per patient was not significantly different between the two arms in any one year. Mean total cost was lower in group 1, the intervention group in year one but rose to slightly above group 2 in year 2 but remained below the control arm in year 3, and above in years 4 and 5.

A iii) As A ii) but excluding costs of CVD deaths[5].

[5] While the intention was to explore the effects of omitting the costs associated with dying from CVD, the results presented here refer to those from excluding the costs of all patients who died. While we intend to refine the analysis to the former, we doubt that it will make any difference to the results.

The exclusion from the costs of those who had died from CVD again changed the cost per patient data as expected but left the pattern and the statistical results unchanged (Table A5).

B) Exposure analysis

The cost per patient in each of the five groups is shown in Table 1, indicating the same pattern as the ITT analysis:

- no significant differences in total cost per patient between the groups with one or more years exposure compared to each other
- cost per patient were higher for than for those with zero exposure compared to those with some exposure, but this difference was not statistically significant
- in each group with some degree of exposure, the increased cost of prevention was offset by reductions in NHS inpatient costs
- since in none of the groups was the cost per patient per year associated with the intervention above that of the control group, cost effectiveness analysis is not necessary.

Table 1

Cumulative total mean cost per patient over 5 years by duration of exposure to secondary prevention clinic

Exposure	No,	Mean £
0	245	4,097
1	309	3,634
2	298	3,083
3	304	3,290
4	187	3,531

Notes: the figures for exposure refer to the number of years of exposure each patient had to secondary prevention clinics.

The mean cost per patient was higher in the group for whom there was no exposure data – these were mainly patients who died, which explains their slightly raised costs.

The differences between the cumulative mean costs per patient were tested using bootstrapping, and no statistically significant differences were found (see Appendix Table).

DISCUSSION

Policy

People with pre-existing coronary heart disease are at particularly high risk of coronary events and death, but effective secondary prevention reduces this risk. Effective secondary prevention comprises several elements. These include pharmaceutical interventions (antiplatelet agents, statins, beta-blockers and angiotensin converting enzyme inhibitors) and interventions to change behaviour and modify lifestyle (smoking cessation, regular exercise and healthy diets).[1] Most studies of secondary prevention have been drug trials which focus on only some of these elements.

As most people with coronary disease are cared for in primary care, general practitioners have been encouraged to target them for secondary prevention.[2] This has proven difficult, however, with surveys of baseline provision consistently demonstrate that secondary prevention is sub optimal. The National Service Framework for CHD in England requires practices to provide secondary prevention.

Several attempts at multifactorial interventions to improve secondary prevention have now been evaluated. A recent systematic review of randomised trials concluded that disease management programmes improved processes of care, reduced admissions to hospital, and enhanced quality of life.[6] No impact on survival or coronary event rates was detected however, probably because the median follow up of studies in the review was too short (one year). A systematic review of 12 randomised trials in a variety of settings concluded that they improved processes of care and risk factors [3].

One trial included in the review which was set in UK general practice reported no benefits[7]. It was, however, limited to patients after a cardiac hospital admission (in whom levels of secondary prevention were already good), so excluded the majority of patients with coronary disease in general practice (in whom uptake of secondary prevention is lower).[4] In a more recent randomised trial in Warwickshire, nurse led secondary prevention clinics were found to improve care by more than recall to general practitioners and audit with feedback.[8] The main limitation with these and most previous studies, however, has been too short follow up to detect effects on mortality or coronary event rates. In one previous randomised trial of health promotion to patients with angina in Belfast, total mortality rates at five years were similar to ours (13.7% and 18.8% in intervention and control groups respectively) but their numbers were smaller, so this difference was not statistically significant.[9] [10] [7]

[6] McAlister FA et al. Randomised trials of secondary prevention in coronary heart disease: systematic review. BMJ 2001, 323: 957-962.
[7] Jolly K et al. randomized controlled trial of follow up care in general practice of patients with myocardial infraction and angina: final results of the Southampton integrated care project (SHIP). BMJ 1999, 318:706-711.
[8] Moher M et al Cluster randomized controlled trial to compare three methods of promoting secondary prevention of coronary heart disease in primary care. BMJ 2001, 322, 1338-42.
[9] Cupples ME et al Randomised controlled trial of health promotion in general practice for patients at high cardiovascular risk. BMJ 1994 309, 993-6
[10] Cupples ME et al Five year follow up of patients at high cardiovascular risk who took part in a randomized trial of health promotion. BMJ 1999 319: 687-8.

The background to the present study was that evidence was needed from longer-term follow up studies on whether improvements in processes of care translate into reduced coronary event and mortality rates.

The benefits found in this study to total mortality and coronary events are consistent with projections made prospectively (by NC and PM) based on the one year effects on secondary prevention, which forecast risk reductions in the intervention group compared to control of 17% for coronary events and 15% for total mortality.[19] They occurred despite improved secondary prevention in the control group after the original intervention year, which shows the value of starting secondary prevention sooner rather than later.

It seems likely that the improvements in secondary prevention seen in the control group between one and four years were due, at least in part, to exposure to secondary prevention clinics. Results of the exposure analysis, by length of exposure to clinics, support this view, since, for the medical components of secondary prevention, longer duration of attendance at clinics was associated with better secondary prevention.[11]

The policy conclusion seems to be that nurse-led clinics in primary care reduce mortality rates of patients with coronary disease by promoting medical and lifestyle components of secondary prevention.

Health economics methods topics

The following points are of interest:

a) implications of ITT for economic analysis
b) implications of exposure analysis
c) the aggregation of statistically significant cost elements with those that are not
d) the focus on disease specific or all cause knock on effects
e) the role of deaths in costs[12].

Implications of ITT for economic analysis

The health results reported here for both 12 months and four years were based on ITT, as recommended by the key texts on trial design and as required for drug licensing. The rationale of ITT has to do with avoiding bias by ensuring estimates of effect are conservative. Thus the denominator is all patients originally randomised, rather than those on whom data are collected, which would exclude drop outs[13]. Thus ITT tends to underestimate effects by attributing no benefit to those on whom no data are available.

[11] On the other hand, there was no association between attendance at clinics and healthier lifestyles. At one-year follow up, the clinics had improved diet and exercise, albeit by a small amount, so the absence of an association at four years needs explanation. It is possible that this is related to changes in the clinic protocol made by most of the practices. In particular, most practices had reduced the frequency of clinic attendance to annual, and this is probably insufficient to promote and maintain lifestyle change.

[12] Since bootstrapping is increasingly recommended for the estimation of cost confidence intervals we explored the difference this would make compared to conventional t tests. For the only cost item likely to be statistically significant differences was the intervention cost, a comparison of bootstrapping and 'raw' p values indicated that both methods gave the same results in all but one year and that the p values were generally higher (less significant) with bootstrapped values. Acknowledging that this was not a good dataset with which to compare bootstrapping with more conventional methods, we have minimised the discussion of this topic.

[13] Last observation carried forward is commonly used but can bias the results.

If in estimating cost effectiveness ratios one wanted to be conservative as befits ITT, one would want to overestimate not underestimate costs. Underestimation of both benefit and costs would lead to CE ratio which is somewhere between the conservative and optimistic. From a resourcing and costing perspective, one would want data on the service use of those on whom data may not usually be available (whether due to death or drop out).

The extent to which data on resource might not be available on such 'missing' patients depends on the methods used: low if based on patient or carer reports (as is commonly the case in RCTs), high if based on routine data sources (as was the case in this study). In this study, 228 patient were lost to death in Scotland and 17 due to other reasons (moved out of Scotland). We were able to obtain data on the NHS inpatient resource use of all (but one) of those who still lived or who had died in Scotland.

We were surprised to find no discussion of this issue of ITT and possible bias in CE ratios in any of the standard texts on economic evaluation (Gold[14], Drummond [15] Glick [16]). To some extent this problem of ITT and costs would only arise if an incremental cost effectiveness ratio was being estimated. However, given the use of ITT in the analysis of benefits, we thought we should follow the cautious spirit in costing. Mean cost has been shown in terms of strict ITT based on the original number randomised, then based on the number of survivors at the mid point of each year. As expected due to the reduced denominator, the mean cost was higher for later years in the latter analysis. We suspect this is the appropriate figure to report but would welcome comments.

An objection might be raised to the use of ITT in the years after the trial had ended, given the cross over of control patients into the intervention group. However this applies only to years 3,4 and 5 as the ITT analysis for year 2 above shows the results of the trial, which shows the same results as for the other years. ITT, it could be argued, may be appropriate for analysis of the trial and exposure analysis for the follow up.

Exposure analysis

Exposure analysis was attractive given the extent of 'cross-over' in this follow up study, which meant that patients had different numbers of years of follow up. Duration of exposure to prevention (coming back annually to the nurse led secondary prevention clinic for advice and to, have medications adjusted) seemed likely to lead to improved uptake of secondary prevention. The dilution of the treatment effect in ITT could be overcome by directly comparing those with some to no exposure. The degree to which the increased costs of secondary prevention were offset by reduced coronary events over time could be explored.

[14] Gold MR. Sigel JE, Russell LB, Weinstein MC Cost effectiveness in health and medicine. OUP 1996.
[15] Drummond MF, Stoddart GL, Torrance GW Methods for the economic evaluation of health care programmes. OUP, 1987.
[16] Glick HA, Polsky DP, Schulman KA Trial based economic evaluations: an overview of design and analysis in Economic evaluation in health care. Merging theory with practice. Drummod M, McGuie A, eds. OHE. Oxford. 2002.

Problems included:

- the healthy attender effect (well survivors more likely to attend clinics)
- some of those who died might have been exposed but data collection on drug use and clinic attendance was incomplete for this group
- other confounding effects due to non-randomisation between groups.

If the results of the exposure cost analysis had been different from that of ITT, we would have had problems as to which approach to prefer. As shown above, the results did not differ by approach, the problem did not arise. However, this is an issue that deserves attention in the health economics literature.

Aggregation of cost elements that are and are not statistically significant

The aggregation of statistically significant differences in some cost headings (cost of intervention) with others that lacked statistical significance (particularly NHS inpatient costs) to give a total cost per patient that was not statistically significant left us wondering about generalisability. Although this is standard practice in economic evaluations, the statistical legitimacy of this relies on the distributions of each cost element being essentially the same (normal). The costs of secondary prevention were spread fairly equally (normally) among those in receipt of it. However, the distribution of hospital admissions (both CVD and non CVD) was skewed.

The sample size, we note was relatively large, and sufficient to capture at the 5% level differences in deaths but not in coronary events[17]. The extent to which costs of NHS admissions were averted was not a prior hypothesis and so was not built into the design of this study. The difference in NHS inpatient cost per patient between the arms was reduced, we note, by the use of ITT in the four years of follow up. The use of exposure analysis however confirmed the results of the ITT analysis.

Although we have shown no statistically significant difference in costs between the groups, can we definitively conclude that there is no difference in costs? For example, based on the confidence intervals, the intervention could have cost up to £200 per patient per year, compared to its mean cost of around £50 per year.

The focus on disease specific or all cause knock on effects

The original study focused on ischemic heart disease (IHD). However, the interventions that comprise secondary prevention for IHD can be expected to have effects outside IHD, notably blood pressure reducing medications (but also probably cholesterol reducing) that reduce not only the risk of cardiac events but also

of strokes. For that reason we broadened the focus to cerebrovascular disease, that is we considered hospitalisations and deaths that were to do with CVD.

By collecting data on all NHS hospitalisations we were able to look at admissions both attributable to CVD and to all other causes, not only over the period of the trial but also in the year before. This showed that while CVD admission rates were similar in each arm in the year before the trial, they were higher for all other causes in the control group. This pattern persisted in succeeding years, in which the CVD admissions in the control group exceeded those in the intervention arm.

The conventional disease specific focus would ignore these raised non CVD admissions. We note the differences but are left with the issue of whether and how these might be included in the analysis.

The role of deaths in costs

The primary outcome measures in the original RCT were effects on uptake of secondary prevention. In the follow up, they were total deaths and coronary events. The differences in total mortality were statistically significant. The differences in the combined endpoint of nonfatal MIs and coronary deaths were borderline.

We wanted to explore the degree to which the costs in the control group were raised by inclusion of deaths which were higher in that group. As deaths incur costs and everyone eventually dies, a case can be made for excluding the costs of death from cost effectiveness analysis (Gold et al, 1996). We explored the implications of excluding CVD deaths for cost per patient comparisons by omitting the costs of those patients who died.

Exclusion of these costs had little effect on mean costs, and the differences did not affect the lack of statistically significant differences between arms. Part of the reason was that the difference in the absolute numbers of deaths between the arms was small.

Conclusions re methods and costing

We offer a number of conclusions based on the experience of costing the above interventions.

The implications of ITT for costing have received little attention in the literature – we suggest that the cautious spirit of ITT which implies underestimation of benefits also implies overestimation of costs. In practice this may mean use of routine data sources to ensure collection of data on the resources used by patients who have died or dropped out, so as to provide conservative CE ratios. Use of standard ITT

[17] We note the recent publications of 8 year follow up data of the LIPID trial of pravastatin in some 9,000 patients (Lancet May, 2002), which is to be accompanied by an economic analysis.

underestimates both costs and benefits. However, this applies mainly to cost effectiveness analysis, which is not a concern for the present study given the lack of statistically significant differences in costs[18] .

We were unclear from the literature as to whether ITT implies use of the numbers of patients as originally randomised or the survivors in each group in each year. As a consequence we did both analyses and found no differences in statistical significance.

Exposure analysis seemed appropriate given the degree of cross over between the arms after the trial ended, but entailed the possibility of bias. Use of secondary prevention was[19] related directly to duration of exposure. Cost per patient did not differ statistically between the exposure groups but this may have been due to the use of five groups, which reduced the sample size. However, given the lack of statistically significant differences in cost in the ITT analysis, the lack of difference in the exposure analysis was perhaps not surprising.

The aggregation of statistically significant differences in some cost headings (cost of intervention) with others that lacked statistical significance (particularly NHS inpatient costs) to give a total cost per patient that was not statistically significant left us wondering about the robustness of our results. The sample size, we note was relatively large, but was not perhaps large enough to capture at the 5% level differences in costs averted. The extent to which costs of NHS admissions were averted was not a prior hypothesis and so could not have been built into the trial design. The difference in NHS inpatient cost per patient was reduced, we note, by the use of ITT in the four years of follow up, possibly reflecting the cross over of patients into the intervention group.

While the initial trial focused on IHD, we broadened the focus to cover all CVD, since the blood pressure lowering drugs might be expected to have effects on stroke as well as IHD. The numbers of CVD events and hospitalisations were similar in both groups at baseline and lower in the intervention group in subsequent years. However the data available show that hospital admissions for non CVD events were higher in the control than the intervention group at baseline and in all subsequent years. Lacking any rationale as to why the intervention might have any effect on non CVD events we have ignored these events.

As we were concerned that the raised CVD deaths (and in all deaths) in the control group might distort (minimise) the analysis of cost differences, we explored the effects of omitting those costs associated with deaths. Again while this reduced the cost in the control group, it did not achieve statistical significance.

[18] . It could, however, be argued that cost effectiveness analysis might be justified to explore in modelling the worst case scenario from the cost confidence intervals.

[19] shown (in a previous analysis – see footnotes 1 and 2.

Finally, while we would welcome advice and comments on the most appropriate method to use in presenting these results, our inclination is to present the costs based on ITT for the trial, and ITT based on each years survivors for the follow up period with a discussion of sensitivity analysis of the effects of exclusion of deaths and the analysis of exposure which did not alter the conclusions that secondary prevention was cost neutral both in the short and medium term.

Table A1

Cost per patient by cost element, by baseline (year 1) and year of trial (year 2) and group (1= intervention, 2= control), based on ITT as originally randomised

year	Variable	group	N	Lower	Mean	upper	StdErr
1	cdrug	1	673	107	115	124	4.35
1	cdrug	2	670	116	125	135	4.74
1	cdrug	Diff (1-2)		-22	-10	3	6.43
1	nhsinpcs	1	673	275	455	635	91.66
1	nhsinpcs	2	670	248	381	515	67.89
1	nhsinpcs	Diff (1-2)		-150	74	298	114.14
1	outcvdcs	1	673	4	6	9	1.20
1	outcvdcs	2	670	3	5	6	0.84
1	outcvdcs	Diff (1-2)		-1	2	4	1.47
1	prvcs	1	673	0	6	12	3.03
1	prvcs	2	670	0	1	2	0.34
1	prvcs	Diff (1-2)		-1	5	11	3.06
1	othercs	1	673	2	4	5	0.71
1	othercs	2	670	2	3	5	0.69
1	othercs	Diff (1-2)		-2	0	2	0.99
1	totalcs	1	673	438	621	805	93.51
1	totalcs	2	670	413	549	685	69.37
1	totalcs	Diff (1-2)		-157	72	301	116.51
2	cdrug	1	673	164	179	194	7.53
2	cdrug	2	670	141	154	167	6.63
2	cdrug	Diff (1-2)		6	25	45	10.04
2	spccost	1	673	38	40	43	1.31
2	spccost	2	670	0	0	0	0.15
2	spccost	Diff (1-2)		37	40	43	1.32
2	invtcs	1	673	204	219	235	7.79
2	invtcs	2	670	141	154	167	6.63
2	invtcs	Diff (1-2)		45	65	85	10.23
2	nhsinpcs	1	673	190	330	470	71.34
2	nhsinpcs	2	670	305	450	595	73.89
2	nhsinpcs	Diff (1-2)		-321	-120	82	102.70
2	outcvdcs	1	673	3	4	5	0.62
2	outcvdcs	2	670	4	6	8	0.93
2	outcvdcs	Diff (1-2)		-5	-2	0	1.12
2	prvcs	1	673	-1	3	6	1.68
2	prvcs	2	670	-5	7	19	6.10
2	prvcs	Diff (1-2)		-17	-4	8	6.32
2	othercs	1	673	3	4	5	0.68
2	othercs	2	670	2	3	4	0.62
2	othercs	Diff (1-2)		-1	1	3	0.92
2	totalcs	1	673	451	594	737	72.98
2	totalcs	2	670	501	653	804	76.98
2	totalcs	Diff (1-2)		-267	-59	150	106.06

Notes: cdrug = cost of CHD drugs, spcost = secondary prevention clinic co cost, invtncs = intervention cost (= drug cost + secondary prevention clinic cost), nhsinpcs = NHS inpatient costs, outcddcs= NHS outpatient costs, prvcs = private hospital inpatient costs, othercs = other NHS costs, totalcs = total cost. All at per patient level.

Table A2

Cost per patient by cost element, by years of follow up (3,4, and 5) and group (1= intervention, 2= control), based on ITT as originally randomised

3	Cdrug	1	673	199	213	228	7.17
3	Cdrug	2	670	170	183	196	6.53
3	Cdrug	Diff (1-2)		12	31	50	9.71
3	Invtcs	1	673	206	220	234	7.24
3	Invtcs	2	670	180	193	206	6.63
3	Invtcs	Diff (1-2)		8	27	46	9.82
3	Nhsinpcs	1	673	210	339	467	65.52
3	Nhsinpcs	2	670	259	405	552	74.62
3	Nhsinpcs	Diff (1-2)		-261	-67	128	99.27
3	Totalcs	1	673	479	612	746	68.00
3	Totalcs	2	670	490	640	790	76.43
3	Totalcs	Diff (1-2)		-229	-28	173	102.28
4	Cdrug	1	673	231	247	262	8.00
4	Cdrug	2	670	201	216	231	7.70
4	Cdrug	Diff (1-2)		9	31	53	11.11
4	Invtcs	1	673	238	254	270	8.10
4	invtcs	2	670	208	223	239	7.84
4	invtcs	Diff (1-2)		9	31	53	11.28
4	nhsinpcs	1	673	261	404	548	73.01
4	nhsinpcs	2	670	381	557	732	89.33
4	nhsinpcs	Diff (1-2)		-379	-153	74	115.32
4	totalcs	1	673	562	708	854	74.45
4	totalcs	2	670	647	827	1,007	91.66
4	totalcs	Diff (1-2)		-350	-119	113	118.04
5	cdrug	1	673	264	283	302	9.75
5	cdrug	2	670	228	247	266	9.67
5	cdrug	Diff (1-2)		8	35	62	13.73
5	invtcs	1	673	271	290	309	9.87
5	invtcs	2	670	237	256	275	9.83
5	invtcs	Diff (1-2)		7	34	61	13.93
5	nhsinpcs	1	673	362	576	791	109.17
5	nhsinpcs	2	670	382	585	789	103.72
5	nhsinpcs	Diff (1-2)		-304	-9	286	150.60
5	outcvdcs	1	673	5	8	10	1.34
5	outcvdcs	2	670	5	7	9	1.14
5	outcvdcs	Diff (1-2)		-3	1	4	1.75
5	prvcs	1	673	-5	7	19	6.04
5	prvcs	2	670	-2	6	14	3.97
5	prvcs	Diff (1-2)		-13	1	16	7.24
5	othercs	1	673	2	3	4	0.60
5	othercs	2	670	1	2	3	0.51
5	othercs	Diff (1-2)		-1	1	2	0.79
5	totalcs	1	673	696	916	1,136	111.94
5	totalcs	2	670	678	887	1,096	106.57
5	totalcs	Diff (1-2)		-274	29	332	154.57

Table A3

P values for differences in mean cost per patient by type of cost, based on bootstrapping (with P values based on T test for comparison)

year	Variable	T-test P value	Bootstrap adjusted P-value
1	cdrug	0.13	0.44
1	spccost	1.00	1.00
1	invtcs	0.13	0.44
1	nhsinpcs	0.52	0.96
1	outcvdcs	0.30	0.78
1	prvcs	0.09	0.30
1	othercs	0.69	0.99
1	totalcs	0.54	0.96
2	cdrug	0.01	0.06
2	spccost	0.00	0.00
2	invtcs	0.00	0.00
2	nhsinpcs	0.24	0.81
2	outcvdcs	0.04	0.16
2	prvcs	0.51	0.99
2	othercs	0.38	0.95
2	totalcs	0.58	1.00
3	cdrug	0.00	0.01
3	spccost	0.00	0.00
3	invtcs	0.01	0.03
3	nhsinpcs	0.50	0.98
3	outcvdcs	0.91	1.00
3	prvcs	0.14	0.57
3	othercs	0.29	0.87
3	totalcs	0.78	1.00
4	cdrug	0.01	0.03
4	spccost	0.81	1.00
4	invtcs	0.01	0.03
4	nhsinpcs	0.19	0.68
4	outcvdcs	0.71	1.00
4	prvcs	0.71	1.00
4	othercs	0.35	0.91
4	totalcs	0.31	0.88
5	cdrug	0.01	0.04
5	spccost	0.04	0.19
5	invtcs	0.02	0.07
5	nhsinpcs	0.95	1.00
5	outcvdcs	0.67	1.00
5	prvcs	0.85	1.00
5	othercs	0.30	0.87
5	totalcs	0.85	1.00

Table A4

Mean cost per patient using number of patients originally randomized and number of survivors at mid point of each year. (Cost headings as in table A1.)

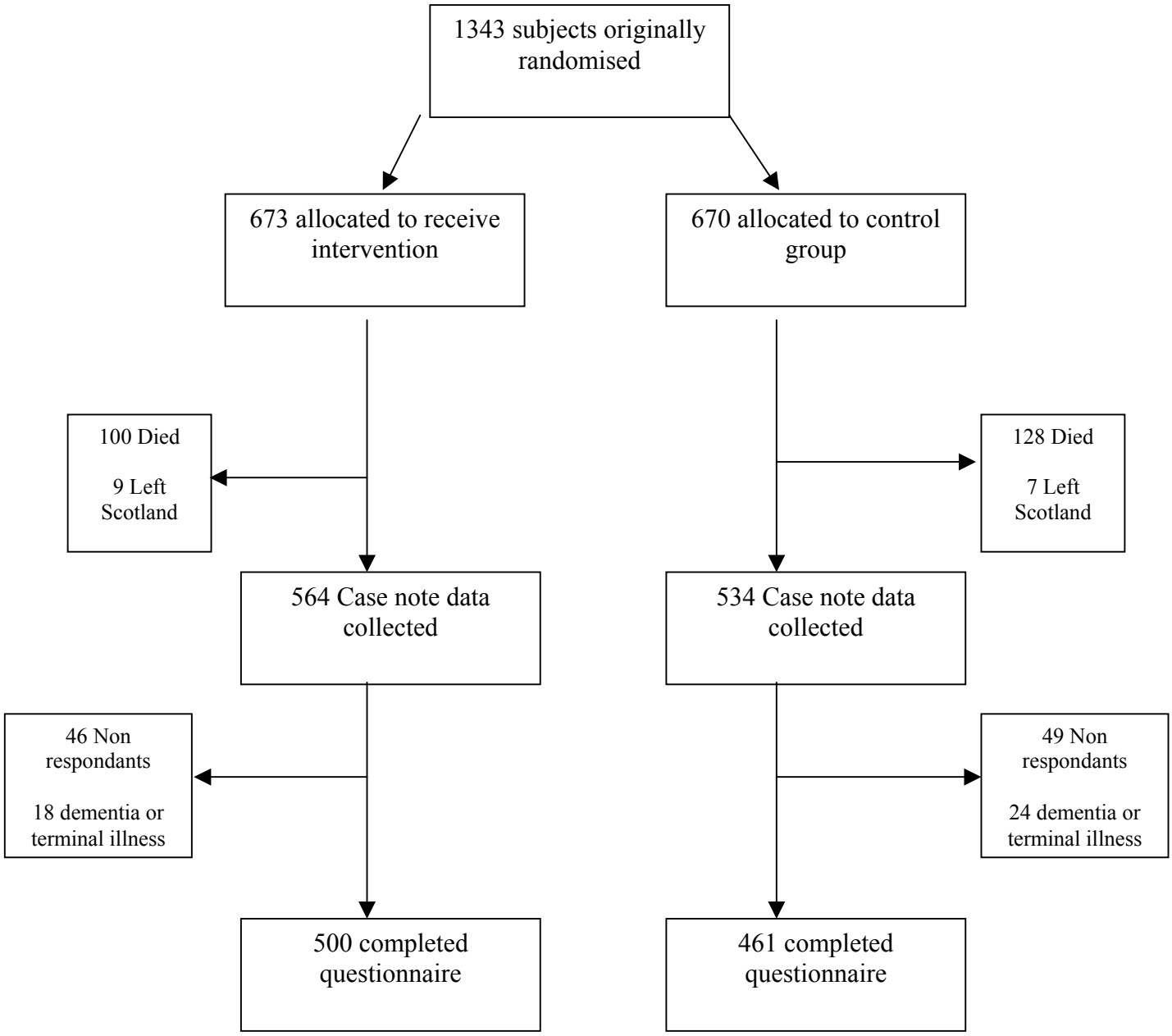
Total summary										
year	group	_FREQ_	cdrug	spccost	invtcs	nhsinpcs	outcvdcs	prvcs	othercs	totalcs
1	1	673	77,729	0	77,729	306,359	4,223	4,114	2,590	418,145
1	2	670	83,891	0	83,891	255,589	3,180	579	2,310	368,009
2	1	673	120,662	27,020	147,682	222,356	2,529	1,886	2,730	399,809
2	2	670	103,137	140	103,277	301,707	4,095	4,640	2,170	437,234
3	1	673	143,655	4,490	148,145	227,921	3,164	7,004	2,458	412,059
3	2	670	122,459	6,870	129,329	271,481	3,237	579	1,862	429,064
4	1	673	166,029	5,050	171,079	272,060	4,561	4,057	2,220	476,571
4	2	670	144,531	5,150	149,681	373,073	4,920	2,807	1,718	553,941
5	1	673	190,224	4,920	195,144	387,882	5,092	4,833	2,170	616,595
5	2	670	165,657	5,890	171,547	392,187	4,567	3,921	1,610	594,277
MEAN COST WITH SURVIVAL AS DENOMITOR										
year	group	N	cdrug	spccost	invtcs	nhsinpcs	outcvdcs	prvcs	othercs	totalcs
1	1	673	115	0	115	455	6	6	4	621
1	2	669	125	0	125	382	5	1	3	550
2	1	661	183	41	223	336	4	3	4	605
2	2	660	156	0	156	457	6	7	3	662
3	1	634	227	7	234	359	5	11	4	650
3	2	628	195	11	206	432	5	1	3	683
4	1	610	272	8	280	446	7	7	4	781
4	2	602	240	9	249	620	8	5	3	920
5	1	587	324	8	332	661	9	8	4	1,050
5	2	568	292	10	302	690	8	7	3	1,046

Table A5

Excluding costs of patients who died: p values for differences in mean cost per patient by type of cost, based on bootstrapping (with P values based on T test for comparison)

year	Variable	T-test P value	Bootstrap adjusted P-value
1	cdrug	0.13	0.45
1	spccost	1.00	1.00
1	invtcs	0.13	0.45
1	nhsinpcs	0.52	0.96
1	outcvdcs	0.30	0.80
1	prvcs	0.09	0.31
1	othercs	0.69	1.00
1	totalcs	0.54	0.96
2	cdrug	0.01	0.05
2	spccost	0.00	0.00
2	invtcs	0.00	0.00
2	nhsinpcs	0.30	0.87
2	outcvdcs	0.05	0.23
2	prvcs	0.52	0.99
2	othercs	0.37	0.95
2	totalcs	0.68	1.00
3	cdrug	0.00	0.01
3	spccost	0.00	0.00
3	invtcs	0.01	0.03
3	nhsinpcs	0.50	0.99
3	outcvdcs	0.91	1.00
3	prvcs	0.14	0.55
3	othercs	0.25	0.83
3	totalcs	0.77	1.00
4	cdrug	0.01	0.03
4	spccost	0.74	1.00
4	invtcs	0.01	0.03
4	nhsinpcs	0.11	0.47
4	outcvdcs	0.56	0.99
4	prvcs	0.72	1.00
4	othercs	0.29	0.85
4	totalcs	0.20	0.71
5	cdrug	0.02	0.11
5	spccost	0.02	0.07
5	invtcs	0.04	0.15
5	nhsinpcs	0.94	1.00
5	outcvdcs	0.67	1.00
5	prvcs	0.87	1.00
5	othercs	0.33	0.90
5	totalcs	0.90	1.00

Figure A1


1343 subjects originally randomised
673 allocated to receive intervention
670 allocated to control group
100 Died
9 Left Scotland
128 Died
7 Left Scotland
564 Case note data collected
534 Case note data collected
46 Non respondants
18 dementia or terminal illness
49 Non respondants
24 dementia or terminal illness
500 completed questionnaire
461 completed questionnaire