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Multi-centre cluster randomised trial comparing a community group exercise programme with home based exercise with usual care for people aged 65 and over in primary care

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Short title: Promoting physical activity in people aged 65+

Acronym: ProAct65+

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TRIAL PERSONNEL AND CONTACT DETAILS

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Trial Coordinating Centre: University College London

SYNOPSIS

Title	Multi-centre cluster randomised trial comparing a community group exercise programme with home based exercise with usual care for people aged 65 and over in primary care
Acronym	ProAct65+
Short title	Promoting physical activity in people aged 65+
Chief Investigator	Professor Steve Iliffe
Objectives	(1) To determine the effect on continuation of exercise of two evidence based exercise programmes designed for older people, compared with usual care i.e. with no special interventions to promote physical activity. (2) To determine the health benefits of the programmes to patients starting at various levels of physical activity, particularly the effects on physical and psychological status, health status and quality adjusted life years (QALYs). (3) To estimate the costs of the exercise interventions and to assess the cost-effectiveness of community group exercise, and home-supported exercise compared with usual care. (4) To determine the acceptability of the programmes, adherence rates, enabling factors and barriers to future implementation. (5) To determine participants' perceptions of the value of exercise, and the predictors of continued exercise.
Trial Configuration	A cluster controlled trial using minimisation for allocation at the level of general practice in two centres (London and Nottingham/Derby),
Setting	Primary care
Sample size estimate	SAMPLE SIZE is based on numbers needed to detect differences in proportions reaching physical activity (PA) targets and quality of life measured by the EQ-5D. Under individual randomisation a small effect size (0.3) equivalent to mean differences 0.05 on the EQ-5D index in community samples requires 176 patients per study group (Roset 1999), and 215 patients are required to detect the difference between study groups of 14.6% and 4.9% achieving PA targets (Elley 2003) (2-sided a=0.05, 1-b=0.90). Data from 24 practices in the British Regional Heart Study suggested an intra-class correlation coefficient (ICC) not exceeding 0.02 for PA among middle aged men (Morris 2001). ICCs collected in primary care settings have typically averaged 0.01 (Adams 2004). With a minimum practice sample after losses to follow up of 30 patients; a design effect of 1.29 based on an ICC of 0.01 to account for cluster randomisation and 30% attrition, up to 1200 patients (400 in each study arm) will be recruited from 30 practices (three groups of 200 patients/5 practices on each site in London and Nottingham/Derby.
Number of participants	1200 in total, 400 in each arm
Eligibility criteria	Eligible patients will be those aged 65+ who can walk around independently indoors and outdoors (with or without a walking aid) and would be physically able to take part in a group exercise class, who are not already receiving any long term physiotherapy and who do not fulfil the exclusion criteria.

Description of interventions	***Home based exercise programme (OEP)*** This exercise programme consists of a 30 minute programme of leg muscle strengthening and balance retraining exercises progressing in difficulty to be performed at home at least three times per week, plus participants will be advised to walk at least twice per week for up to 30 minutes at a moderate pace, for 24 weeks. Trained peer mentors will contact and visit the patients at their home to start the exercise programme with them and will follow-up with up to three more home visits / exercise sessions as the participants require ***Community based exercise programme (FaME)*** FaME consists of one hour long PSI delivered group exercise class in a local community centre for a maximum of 15 participants, and two 30 minute home exercise sessions (based on the OEP) per week, for 24 weeks. Participants will also be advised to walk at least twice per week for up to 30 minutes at a moderate pace. ***There will also be a 'treatment as usual' group***
Duration of study	Four and a half years from June 1st 2008, two and a half years per participant.
Randomisation and blinding	Practice staff will also be advised that they will not be informed of the practice's study group allocation until after they have given consent to take part in the study, and all eligible patients from the practice have been recruited.
Outcome measures	**Primary Outcome** Proportions reaching the recommended physical activity (PA) target of at least 30 minutes of activity of moderate intensity on at least 5 days each week, measured using the CHAMPS, PASE and Phone_FITT questionnaires. The proportion reaching the recommended target will be compared between treatment groups using random effects logistic regression to estimate odds ratios and 95% CI. **Secondary Outcomes** will include: 1. The direct health benefits i.e. functional and psychological status; the rate of falls and the number and nature of falls, and fear of falling. 2. Stage of change, self efficacy for exercise and physical self-perception (self-esteem relative to the physical domain), which includes measurement of perceived importance (the degree to which participants value their physical condition, body image and physical strength) to inform predictors of exercise adherence and continuation, and participants' judgement of the value or importance of physical activity. 3. Quality adjusted life years (QALYS), using SF-12 scores transformed into EQ-5D utility weights. 4. The direct costs of delivering both exercise programmes, and the cost offsets identified from a comparison of the health and social service utilisation of participants in all groups during the study period.
Statistical methods	***Proposed Statistical Analysis*** Characteristics of participants and practices will be compared descriptively at baseline. Comparisons between treatment arms will be made using random effects models to allow for clustering between practices and will be undertaken on an intention to treat basis. Linear regression models will be used for continuous outcome variables, logistic models for binary outcome variables, and Poisson or negative binomial models for data on rate of falls. The assumptions for using each model will be checked and analyses adjusted accordingly. All analyses will be undertaken, adjusted (a) for variables used for minimisation (centre, deprivation and practice size), (b) for baseline values of the outcome measure, and (c) variable imbalances at baseline if necessary. Differential effects of the intervention by age, sex and baseline activity levels will be assessed for the primary outcome measures by adding terms for the interaction between age, sex and baseline activity levels and treatment arm to the regression models.

Proposed Economic Analysis

The analysis will adopt standard techniques of economic appraisal (Drummond 2005). The resources used in the delivery of the interventions will be collected from records kept by PSI instructors (FaME) and the research associate and mentors (OEP). The use of facilities (FaME) and equipment, and the time spent on travel and instruction will be included and monetary costs will be assigned according to market rates. Travel costs of PSI instructors and participants (FaME) and peer mentors (OEP) will also be collected.

In addition, the use of health and social care services (GP, outpatient, hospital admission,) will be collected for participants in all groups. Self reported service utilisation will be verified from GP records. Costs of services will be obtained from local and national sources (Curtis and Netten, 2008). Health and social care costs in the exercise groups will be compared with each other and with the usual care (no exercise) group to assess the extent to which the costs of the exercise intervention are offset by savings elsewhere in the health and social care system.

The main outcome measure for the economic analysis will be quality adjusted life years (QALYs). If statistically significant differences between groups are found, incremental cost effectiveness ratios will be calculated to show the extra cost incurred per QALY gained. Comparisons will be conducted between the usual care group and each type of exercise programme, and between the two interventions, using group means of QALY changes and costs. Bootstrap methods will be used to represent uncertainty of estimates, either for constructing confidence intervals or probability curves. Secondary cost-effectiveness analyses will be conducted using physical activity and other outcomes as the measures of effectiveness.

Sensitivity analyses will investigate the cost-effectiveness of the interventions for people with different levels of physical activity, health status and health related quality of life at baseline. The impact of uncertainties in the estimation of costs and outcome variables will also be explored using one way and probabilistic sensitivity analysis.

ABBREVIATIONS

Add to / amend accordingly

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
DAP	Data Analysis Plan
DMG	Data Monitoring Group
EOT	End of Trial
FaME	Falls Management Exercise Programme
GCP	Good Clinical Practice
ICF	Informed Consent Form
OEP	Otago Exercise Programme
NHS	National Health Service
PCT	Primary Care Trust
PI	Principal Investigator at a local site
PIS	Participant Information Sheet
PSI	Postural Stability Instructors
QALY	Quality Adjusted Life Years
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
TMG	Trial Management Group
TSC	Trial Steering Committee

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TRIAL BACKGROUND INFORMATION AND RATIONALE

The health benefits of physical activity have been extensively reviewed and evidence suggests that it reduces the risk of cardiovascular disease, type 2 diabetes, osteoporosis and certain cancers (DOH 2004). There is growing evidence of the association between regular physical activity and a reduced risk of all cause mortality (Blair 1996), and of the potential savings from exercise promotion for older adults for NHS Budgets (Nicholl 1994). Falls are also common in people aged 65 years and older and can have serious consequences, including injury, pain, impaired function, and loss of confidence in carrying out everyday activities, loss of independence and autonomy, and even death (Skelton 2004, Close 2005). There is evidence that interventions providing some form of exercise may be effective in preventing falls amongst older people (Gillespie 2005) and that healthcare costs (Lawrence 2005, Newton 2006) can be reduced if falls are reduced (Tinetti 1989, Cryer 2001, Robertson 2001, NICE Guidelines 21 2004, Close 2005).

Current recommendations for health benefits are that people do at least 30 minutes of physical activity of moderate intensity on at least five days of the week (DoH 1996). However, surveys have consistently shown a high prevalence of physical inactivity in the UK population (Skelton 1999, Joint Health Surveys Unit, 1999). A recent systematic review compared seventeen randomised controlled trials with different interventions designed to encourage sedentary, community dwelling adults to do more physical activity (Hillsdon 2005). Interventions varied widely and included counselling (individually or in groups), self directed or prescribed, supervised or unsupervised, and home-based or facility-based physical activity. Although there was marked clinical heterogeneity in the interventions used, the conclusions were that they could be effective in the short and mid term, at least in middle age, and that there were no significant increases in adverse events for intervention participants in the four studies that reported them. However, the most effective individual intervention (e.g. home-based or facility based) in increasing physical activity in the long term, or in specific groups (e.g. older age) remained uncertain. Habitual physical activity is notoriously difficult to measure by questionnaire (Jørstad-Stein 2005) but quantitative body fixed sensors are not practical for large trials.

The NHS is attempting to address the problem of inactivity in a variety of ways, including exercise referral schemes in primary care (also known as ‘exercise on prescription’ which usually involves referring patients to local leisure centres). Exercise on prescription schemes are currently provided by approximately 89% of Primary Care Trusts (DoH 2005). Relative frailty is not necessarily a barrier to exercise promotion, as referral for exercise has been shown to be feasible and effective in vulnerable older people (Dinan 2006). Despite this, older people may experience significant barriers to the uptake of exercise classes in leisure centres and for many older people home exercise or group exercise in non-intimidating environments (e.g. community halls) may be more appealing, and result in higher uptake of exercise programmes and longer continuation of exercise.

The OEP (Otago Exercise Programme) and FaME (Falls Management Exercise) exercise programmes were both designed for use in community settings specifically for older people aged 65 and over. As well as being designed to reduce falls in older people, both are based on the components of fitness and principles of programming for all older adults (warm up, mobility, stretches, strength and balance, endurance and a cool-down) and have all the elements of training appropriate for that age group. Exercises are tailored for the individuals’ ability and health need. Both the OEP and FaME programmes concentrate on strength and balance training. Strength training is important for older adults because of the wider benefits that are seen to immune and endocrine function, mobility and activities of daily living (Skelton 2003).

The OEP is an individually tailored home based exercise programme for older people, which was developed at the University of Otago Medical School in New Zealand. Its contents are described in the section called ‘planned interventions’. It has been shown to be effective in reducing the number of falls and fall-related injuries, improving balance and strength, improving confidence in performing everyday activities without falling, and was also shown to be cost effective for the oldest old (aged 80 and over) (Campbell 1997,1999, Gardner 2001, 2002, Robertson, Devlin 2001, Robertson 2002). It was designed to be delivered by physiotherapists and nurses trained by, and supervised by physiotherapists. Whilst it has been shown to be effective in four controlled trials of older primary

care patients in New Zealand, it has not been tested in a primary care setting in the UK for feasibility, impact, acceptability and cost-effectiveness.

FaME is a group exercise programme which was developed and tested in a controlled trial in the UK (Skelton 2005), but not in a primary care population. It includes and extends the OEP, aims to reduce asymmetry as well as improve balance (Skelton 2002) and was designed to be delivered by qualified postural stability instructors (PSIs). Its contents are described in the section called 'planned interventions'. FaME has been evaluated in people aged 65-95 and has been shown to be effective in reducing the number of falls, the number of injuries resulting from falls, and preventing further falls (Skelton 1999, Skelton 2005). FaME needs to be evaluated for its impact, acceptability and cost-effectiveness within primary care.

OEP evaluated as a one year intervention showed considerable improvements in outdoor activities after 6 months (unpublished data Campbell) with participants continuing to exercise after completing the programme. Participant support strategies i.e. home visits, telephone follow-up are an important part of the programme. Separately, peer mentors have been shown to almost double both uptake and adherence to long term physical activity amongst older people (Stewart 1997, 2001, 2006). With minimal training, voluntary peer mentors could support and encourage adherence to the OEP home exercise and the walking plan. Evaluation of FaME showed good compliance and nearly two thirds of people participating in FaME continued in group exercise programmes for over a year after trial completion, and although FaME was tested as a 9 month intervention significant improvements in confidence and quality of life were found after 6 months (unpublished data Skelton).

Both FaME and OEP have already been introduced into practice. There are over 800 qualified PSI Instructors (NVQ Level 4 Specialist Exercise Instructor status) on the Register of Exercise Professionals in the UK. The qualification and FaME training programme, funded initially by the Department of Health and accredited and externally verified by the University of Derby, are well established, with 45 courses already run, and 10 more planned for 2007. Links have also been established with appropriate community venues. The Senior Peer Mentor Physical Activity Programme for Older People based on the CHAMPS program (Stewart 1997, 2001) which was funded initially by the Department of Health and the Department for Education and Skills Adult Learning Section, was successfully piloted and shown to be not only economical, but also effective in promoting adherence to physical activity. The programme is currently being implemented in 20 local sites across the UK involving over 400 mentors. Therefore, if the proposed study shows either exercise programme to be effective, the resources are already available for Primary Care Trusts to commission them, and are ready for implementation in many areas.

TRIAL OBJECTIVES AND PURPOSE

PURPOSE
The aim of the project is to evaluate the delivery, impact and cost-effectiveness of a community based exercise programme (FaME); compared to a home based exercise programme (OEP) supported by similarly aged mentors; compared with usual care for primary care patients.

PRIMARY OBJECTIVE
To determine the effect on continuation of exercise of two evidence based exercise programmes designed for older people, compared with usual care i.e. with no special interventions to promote physical activity.

SECONDARY OBJECTIVES
(1) To determine the health benefits of the programmes to patients starting at various levels of physical activity, particularly the effects on physical and psychological status, health status and quality adjusted life years (QALYs).
(2) To estimate the costs of the exercise interventions, and possible cost offsets, and to assess the cost-effectiveness of community group exercise, and home-supported exercise compared with usual care.

(3) To determine the acceptability of the programmes, adherence rates, enabling factors and barriers to future implementation.
(4) To determine participants' perceptions of the value of exercise, and the predictors of continued exercise.

TRIAL DESIGN

TRIAL CONFIGURATION

A cluster controlled trial using minimisation for allocation at the level of general practice in two centres (London and Nottingham/Derby), to compare a community-centre based group exercise programme - FaME [delivered by specifically trained postural stability instructors (PSIs) and supplemented by home exercise and prescriptive recommendations for walking], with a home based exercise programme and walking plan - OEP [supported by specifically trained and similarly aged mentors], with two years follow-up to determine the impact, acceptability and adherence to the programme, and longer term continuation of exercise. Control subjects will continue to receive usual care in primary care. A cost-effectiveness analysis will be conducted within the trial.

Primary endpoint

Proportions reaching the recommended physical activity (PA) target of at least 30 minutes of activity of moderate intensity on at least 5 days each week, measured using the CHAMPS, PASE and Phone_FITT questionnaires. The proportion reaching the recommended target will be compared between treatment groups using random effects logistic regression to estimate odds ratios and 95% CI.

Secondary endpoint

See secondary outcomes (above) and outcome measures (below).

Safety variables and endpoints

Safety variables will include falls risk assessments, vital signs (pulse rate, BP), functional abilities.

Safety endpoints will be falls and significant adverse events (AEs) spontaneously reported during the study and discontinuations due to AEs.

Stopping rules and discontinuation

See risk management procedures (pages 15 and 18).

RANDOMIZATION AND BLINDING

It is important that the concealment of allocation of practices (i.e. to which study arm) is preserved until those practices have committed to the study. It is difficult for participants to be blind in trials of exercise interventions, and for the research associates to be blind to the allocation of participants as they will be involved in patient recruitment and assessments. However, general practices and their patients, and the research associates will not have foreknowledge of the study group allocation of the practice which will not be disclosed until after all patients within a practice have been recruited. Also, for the statistical analysis of participants' data, the statistician will be blind to the study group allocation of the participants.

As soon as a practice has given consent, the research associates will liase with practice staff to produce lists of potentially eligible patients to invite them to participate in the study. Allocation of practices will be carried out by the London centre.

The practices that participate will have to be fully committed to accepting the treatment assignment before it is revealed. They will be given an identification number and treatments will be assigned using computer generated random number tables, embedded in a computer program for minimisation. Treatment assignment will be concealed until all patients are recruited at that practice.

Due to the relatively small number of practices in the trial, minimisation will be used to allocate practices to treatment arms to ensure maximum balance (Pocock 1983). After all the patients from a

practice have been recruited, their practices will be individually allocated to a study arm by the London co-ordinating centre. The variables to be used in the minimisation process will be trial centre (London / Nottingham & Derby), practice size (≥ median practice size / < median practice size) and the index of multiple deprivation 2004 (Noble 2004) (≥ median IMD2004 / < median IMD2004). Minimisation will be undertaken using the MINIM program (Evans et al). Practice recruitment and allocation will be performed concurrently in the two centres.

Maintenance of randomisation codes and procedures for breaking code
N/A

TRIAL MANAGEMENT AND STEERING
The following management groups and steering committee will ensure the timely operation of the trial.

MANAGEMENT

- The Trial Management Group (TMG) meets once every 3 months in the first 3 years and once every 6 months during years 4 and 5. It will include all co-applicants, research associates and user representatives. Communication between meetings will be by email and by teleconferences.
- Centre management groups will meet monthly and include user representatives. The Trial Manager will also routinely attend these management meetings at the Nottingham centre at least every three months, and will be in regular communication with by email and telephone. We will seek honorary contracts with PCTs through their R&D departments for research associates at both centres, and the project will report to PCT R&D departments on the same 6 monthly basis as it will with the HTA.
- Weekly supervision of the research associates and clerical staff will be provided by SI and the Trial Manager in London and DK in Nottingham / Derby; research staff at each site will be in the same campus to facilitate this.

TRIAL STEERING COMMITTEE

The Trial Steering Committee (TSC) will provide a critical overview of the trial, and will meet at the beginning of the trial and then annually, unless the Principal Investigator needs to seek its advice on risk management, in which case a special meeting will be convened. The TSC will include the Principal Investigator and local project leads (SI & DK), independent representatives of relevant voluntary organisations, individuals with expertise in exercise promotion and falls prevention, a statistician, and nominees of the funding body. It will be chaired by an independent investigator with expertise in exercise promotion. The TSC will report to the HTA and advise the TMG. Because no medicinal products are being tested and the risks of the kind of exercise that are being promoted are low, a separate data management and ethics committee will not be convened, but responsibility for overview of the risks of the trial will rest with the TSC.

Terms of Reference (TOR)

Membership
This comprises some members of the TMG and independent members.

TMG members
Professor Steve Iliffe, UCL [CI & PI, London]
Deborah Haworth, UCL [Trial manager]
Professor Denise Kendrick, Nottingham University [Nottingham/Derby PI]
Professor Tahir Masud, Nottingham University Hospitals NHS Trust and University of Derby
Dr. Dawn Skelton
Susie Dinan, UCL
Dr Richard Morris, UCL [Trial statistician, attendance as necessary]
Dr Heather Gage [Trial Economist, attendance as necessary]

Independent members
Gladys Pearson, Research Fellow, Manchester Metropolitan University
Jonathan Treml, University Hospitals Birmingham NHS Foundation Trust
Amy Burchell, Help the Aged and Age Concern England
Professor Ian Philp, University of Sheffield
Amanda Farrin - Statistician, University of Leeds
Representative of the HTA (to be confirmed)

Voting membership of the TSC will be restricted to the CI and site PIs, so that the independent members have the casting vote if necessary.

Overall purpose
To oversee the trial design and conduct to ensure the study governance and conduct complies with good clinical practice (GCP) guidance.

1. To approve the trial protocol and any subsequent amendments to it and to monitor adherence to the protocol
2. To monitor trial progress and to advise on methods for successfully completing the trial within the specified time frame
3. To advise the TMG on patient safety issues including the definition, identification and management of adverse events.
4. To receive email notification from the TMG of serious adverse events.
5. To initiate the setting up of a Data Monitoring Group (DMG) in the event of an excessive serious adverse event rate or if other information is reported to it which raises concern over the safe conduct of the trial. (The DMG would then establish trial cessation criteria, monitor these, and report to the TSC).
6. To consider new information of relevance to the trial such as new studies, and to consider the implications of new information for the conduct of the trial.
7. To advise and support as necessary on other aspects of design or conduct of the trial.

Meetings and Administration etc
1. Meetings will be yearly (minimum) held in rotation in London, Nottingham/Derby.
2. Meetings will be organised and funded by the trial.
3. Minutes of the meeting will be produced by and distributed by TMG administrative staff.
4. Additional E-mail communication will be used as necessary.

DURATION OF THE TRIAL AND PARTICIPANT INVOLVEMENT
Participants will be involved in the trial for two and a half years, including waiting time for practice allocation, 24 weeks of exercise intervention and two years' follow-up.

The trial timetable is as shown in Appendix 5.

The end of the trial will be the end of the follow up period for the last recruited patient.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

General practices will be recruited from the new Primary Care Research Networks (PCRN) of practices in London and Nottingham/Derby. The PCRNs will be asked to identify potential participant practices by size and deprivation status. Past research experience has shown that recruitment is likely to occur in successive waves, determined by practice size and the ways in which invitations to participate are made. For example, larger practices have a slower decision-making process and will take longer to decide whether to participate. It will be necessary to target more practices than required to allow for those who decline. Approaches by mailed invitation, telephone contact with practice managers, and personal contact with local GP opinion leaders may be necessary (Curran 2003, Downs 2006, Wilcock 2007).

A total of 30 practices will be recruited, 15 from each centre. Inclusion criteria will be 1) commitment to participate over the duration of the study and 2) availability of a suitable community venue in the practice catchment area. Practice staff will be briefed on the aims of the study, content and evidence base of the community exercise programme (FaME), the home based exercise programme (OEP), the assessment tools and patient recruitment. To address the risk of post-randomisation recruitment bias, practice staff will also be advised that they will not be informed of the practice's study group allocation until after they have given consent to take part in the study, and all eligible patients from the practice have been recruited.

Recruitment of patients
As soon as a practice has given consent, the research team (research associates/trial manager/site PIs) will liase with practice staff to produce lists of potentially eligible patients to invite them to participate in the study. Eligible patients will be those aged 65+ who can walk around independently indoors and outdoors (with or without a walking aid) and would be physically able to take part in a group exercise class, who are not already receiving any long term physiotherapy and who do not fulfil the exclusion criteria.

Practices will be asked to produce a numbered list of patients aged 65+. Practice staff will be allowed to make and justify their own exclusions in liaison with the research team. The research team will provide the practices with a random number list to select the samples of patients to be approached after exclusions have been made. The sampling will vary depending on practice size. In practices with fewer than 600 patients aged 65 and over (see sample size calculation page 20, all patients aged 65 and over will be invited to participate. In larger practices random sampling will be used to identify 600 patients aged 65 and over to invite to participate. Patients will then be sent letters by their usual General Practitioner containing a study invitation, a study information sheet, a reply slip and a freepost envelope. The invitation will contain a two part consent process: 1) for participation in the study and 2) to allow access to their electronic medical records to capture data for the economic analysis (see page 18). The content of the invitation letter will include all details of the study, and inform the patients of their opportunity to be allocated to one of three groups (FaME group exercise; OEP home exercise; usual care) once they have been screened for eligibility and have given their consent to take part in the study. If, within 2 weeks of the practice posting the invitations the number of replies is under 45, the practice will send out reminder letters to all their patients who were on the first mail-out.

The research associates in both centres will make initial appointments with those patients who have expressed an interest, by telephone. In this phone the research associates will assess current levels of physical activity in order to identify those who are clearly already achieving the target level of exercise. These potential participants will not be invited to an appointment but will be asked to consider becoming peer mentors . At the appointment with those patients who are not exercising at or above the target level, the research associate will provide further information about the study, review their eligibility against inclusion and exclusion criteria and to obtain their consent.

The research associates will be trained in the delivery of the falls risk assessment (FRAT) tool (Nandy 2004), the OEP home exercises and the functional assessments. At the initial appointment the research associates will explain the aim and design of the study and exercise programmes in detail, and the allocation of practices to study groups. They will also obtain consent from the patient or record reasons for their refusal and ask permission to record some anonymised, demographic information for comparison with study participants. Data on age and sex will be recorded for those patients who are approached but decline to attend the initial assessment, to be compared with participants. All consenting patients will then undergo their baseline assessments (functional tests and research questionnaires) and will be given diaries to record falls, exercise, and health and social care on a daily basis. Diaries will be collected every 4 weeks by mail. To determine those patients who are at high risk of falls, the research associates will perform a risk (of falls) assessment using the Falls Risk Assessment tool (FRAT) (Nandy 2004) and Timed Up and Go test (TUG) (Podsiadlo 1991). Patients will be advised that they will be informed of their allocation as soon as all the patients from their practice have been recruited and will be given an indication of when that will be and how they will

be informed. By not allowing general practices and their patients, or the researchers recruiting them to have foreknowledge of the practice's study group allocation the risk of recruitment bias and differential recruitment is reduced.

The research associates will be informed of the practice allocation to notify the participating patients. They will make another appointment or visit patients allocated to home exercise to introduce the exercise programme. FaME group exercise participants will be informed of their exercise venue and timetable.

The timescale for recruiting patients from a consenting practice needs to be as quick as possible so that (1) we reduce the time between receiving patient's consent and notifying them of their allocation to minimise the drop-out rate, and (2) if the practice is allocated to an intervention group the time between the baseline assessment and starting the exercise programme for FaME and OEP participants is kept to a minimum (preferably no longer than one month) so that the baseline measurements for function and health status are still current.

Inclusion criteria

Those aged 65+ who can walk around independently indoors and outdoors (with or without a walking aid) and would be physically able to take part in a group exercise class.

Exclusion criteria

Exclusion criteria will be checked at the recruitment appointment by the research associate. This will include measurement of resting BP and pulse and completion of a health questionnaire. The patients GP will be asked to confirm eligibility for each potentially eligible patient.

Exclusion criteria for the ProAct65+ trial are:

- Three or more falls in the previous year ("frequent fallers");
- Resting BP > 180/100 mmHg; tachycardia > 100bpm; those considered by their GP to have uncontrolled hypertension; significant drop in BP during exercise recorded in the medical records or found at initial assessment;
- Psychiatric conditions which would prevent participation in an exercise class, for example, psychotic illness;
- Uncontrolled medical problems, which the GP considers would exclude patients from undertaking the exercise programme; for example, acute systemic illness' such as pneumonia, poorly controlled angina, acute rheumatoid arthritis, unstable or acute heart failure;
- Conditions requiring a specialist exercise programme, for example, uncontrolled epilepsy, significant neurological disease or impairment; unable to maintain seated upright position or unable to move about independently indoors;
- Not living independently (e.g. residential or nursing care);
- Significant cognitive impairment (unable to follow simple instructions);
- Already receiving long term physiotherapy.

Patients will also be excluded if they are already exercising for 30 minutes or more on 5 or more occasions per week but they will be offered the opportunity to become a peer mentor.

Expected duration of patient participation

Study participants will be participating in the study for no more than 31 months.

Removal of participants from interventions, assessments or the trial

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis.

The research teams at each site will advise discontinuation of exercise intervention or withdrawal from the trial if the exercise intervention poses a hazard to the safety of a patient, or if the patient poses a hazard to the safety of another patient.

Those who withdraw from the trial or follow-up will not be replaced. Participants should not be accepted as lost to follow-up unless 2 phone calls, letters or visits to the participant have been fruitless.

Informed consent

All patients will provide written informed consent. The Informed Consent Form will be signed and dated by the patient before they enter the trial. The research associate will explain the details of the trial and provide a Patient Information Sheet, ensuring that the patient has sufficient time to consider participating or not. The research associate will answer any questions that the patient has concerning study participation.

Informed consent will be collected from each patient before they undergo any interventions (including physical examination and history taking) related to the study. One copy of the Informed Consent Form will be kept by the patient, one will be kept by the research associate, and a third will be retained in the patient's general practice records.

Where a patient who appeared to be eligible and signed a consent form is subsequently found not to be eligible (e.g. the GP considers they fulfil one of the exclusion criteria) prior to the practice being allocated to a treatment group, they will not be considered to have entered to study.

Should there be any subsequent amendment to the final protocol, which might affect a patient's participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

PLANNED INTERVENTIONS

Home based exercise programme (OEP)

This exercise programme consists of a 30 minute programme of leg muscle strengthening and balance retraining exercises progressing in difficulty to be performed at home at least three times per week, and a walking plan to be undertaken at least two times per week for 24 weeks. Each person receives a booklet with instructions for each exercise prescribed and ankle cuff weights (starting at 1kg) to provide resistance for the strengthening exercises. The research associates will be trained to introduce the home exercise programme to participants and give them an appropriate starting level. Trained peer mentors will contact and visit the participants at their home to start the exercise programme with them and will follow-up with up to three more home visits / exercise sessions as the participants require. Volunteers will not have a history of falls in the last year and score 2 or less on the FRAT to be eligible to become peer mentors. As prescribed in the original OEP, patients will record the days they carry out the programme, and in this study the mentors will also telephone them on a regular basis (fortnightly). The support of mentors has been shown to be effective in increasing adherence (Stewart 1997, 2001, 2006). The mentors will be asked to record and report any problems encountered with the exercise programme to the research team using an adverse event form developed for the study (Appendix 3).

In situations where it is difficult to recruit sufficient Peer Mentors to the study the home based exercise programme will be delivered by either Postural Stability Instructors, already working on and familiar with the study, or by younger volunteers. These volunteers will be trained in the delivery of the home based programme. If this contingency plan is put into place the OEP may be delivered in a modified form which will consist of telephone calls only.

Community based exercise programme (FaME)

FaME consists of one hour-long PSI delivered group exercise class in a local community centre for a maximum of 15 participants, and two 30 minute home exercise sessions (based on the OEP) per week for 24 weeks. Participants will also be advised to walk at least twice per week for up to 30 minutes at a moderate pace. The programme includes leg muscle strengthening and balance

retraining that progress in difficulty. Progressive trunk and arm muscle strengthening, bone loading, endurance (including walking) and flexibility training, functional floor skills and adapted Tai Chi complete the evidence based programme. Ankle and wrist cuff weights, therabands and mats are also used throughout the programme. The group exercises include retraining of the ability to get up from the floor (backward chaining) and floor exercises to improve strength, balance and coping strategies to reduce the risk of complications resulting from a long-lie (see Skelton et al.1999). The paper outlining the effects (Skelton 2005) has further information on exercise programme specific exclusion criteria and drop-outs.

PSIs will keep registers of attendance to record each patient's attendance and monitor and record any adaptations to the programme and any feedback from patients. They will follow up non-attenders by telephone as necessary, recording any positive or negative feedback, and notify the research team about reasons for non-attendance or drop-out. Patients will be given a booklet containing their home exercise instructions. As all patients from a practice will be recruited before the allocation of the practice, the group classes will be scheduled at full capacity**.** PSIs are trained to tailor exercises for people of differing abilities and at different points in the progression of the programme within the same exercise class.

Cultural and ethnic sensitivity
With regard to the ethnicity of the study sample, we have considered both cultural and language issues. We will make every effort to accommodate cultural and religious requirements within the exercise programmes. We will utilise the recommendations published in two recent reports from the Help the Aged Minority Ethnic Elders Falls Prevention Programme (MEEFP) www.helptheaged.org.uk/meefp, and liase closely with Skills Active who are working with the Integrated Fitness Initiative's (IFI) current programme: Physical Activity Provision for Ethnic Minority Groups (d.page@ymcafit.org.uk). Some of the FaME and OEP exercise instruments (VHS tape, DVD, booklets) have already been translated (Punjabi (with Urdu inset), Bengali, Cantonese and Hindi) in collaboration with two co-applicants DS/SD.

FaME group classes:

- 2 co-applicants developed the PSI and OEP training courses (DS/SD: OEP in collaboration with the original OEP authors) and they will develop study specific advice on the appropriate clothing and footwear for both exercise programmes. In addition, they will advise on ways in which the Help the Aged /IFI/Skills Active ethnic minorities recommendations can be implemented e.g. participants can adapt their clothing, and the environment can be adapted according to requirements. The recommendations for attire for all exercise classes will respect the cultural and religious issues for a range of ethnic groups. This will be explained in patients' information sheets.
- Where a single-sex environment is a cultural or religious preference, participants will be scheduled to single-sex classes.
- As far as possible exercise venues will provide separate female and male changing areas and/or privacy for changing for those participants who prefer not to change in the company of others. The appropriate attire would be able to be worn to and from the classes if this is an acceptable alternative.
- The exercise classroom will be screened i.e. blinds and windows will be covered for the duration of the class as appropriate.
- Instructors will be allocated as appropriate i.e. female instructors for female only classes and male instructors for male only classes.
- A female instructor will wear neat but not figure hugging clothing with her shoulders and thighs fully covered.
- Music is generally used to welcome participants and set the atmosphere. Any music used will be appropriately selected and lyric free.
- Classes will be timetabled at different times of the day to enable different participants to attend around family and domestic commitments.
- Cultural issues such as family support will be encouraged and facilitated. For example, in previous exercise classes it is common for older female participants to request that their

daughters accompany them in classes which will be perfectly acceptable in the FaME exercise programme.

OEP home exercise:

- Cultural issues such as family support will be respected. At the appointment to introduce the home exercise the research associate will discuss fully the implications and practicalities of a mentor visiting the participant's home to ensure that this is acceptable to the participant and the participant's family. It will also be acceptable for younger family members to participate in the exercise programme in support of the older participant.

The issues and costs of accommodating language barriers with research material, translations and/or interpreters for all possible nationalities and languages is harder to anticipate and accommodate. We propose the following:

- All research material (invitation letters, information sheets, consent forms, research questionnaires) and exercise manuals will be made for a relatively low reading age of 9 years. In this way we will be screening potential participants i.e. if they are able to read and understand the information and response sheets their English should be adequate to take part in the study. Inability to read the material would not be a formal part of the exclusion criteria as the individual may be able to follow movement and correction accurately in classes, and may have help with interpretation (see below).
- If another (possibly younger) member of the potential participant's family helps with interpretation it would be possible to accommodate them in classes and in the home exercise programme if that member acts as an interpreter (see above FaME group classes and OEP home exercise). This would be explained in the patients' information sheets.
- Wherever possible we will provide translations of research material and exercise manuals for those patients who may be able to speak but not read English.

Any other cultural/religious or language barriers to participation will be described in detail as a project outcome in order to aid future implementation of the trial interventions.

Concomitant treatments with medications, physiotherapy for acute conditions, behavioural and other forms of psychological therapy, surgery used during the trial will be documented on the CRF (as well as in the participant's medical records). General practitioners in participating practices allocated to intervention status will be discouraged from referring patients involved in the trial to other exercise therapy projects, outside the study.

Compliance

Compliance will be defined as continuation with exercise regimes. Attendance registers taken during exercise classes by PSIs, record compliance to the FaME exercise programme. Compliance to OEP will be recorded at the peer mentor home visits and fortnightly telephone calls.

Criteria for terminating trial

Stopping the trial as a whole may be as a result of a formal or informal interim analysis and based on overwhelming evidence of efficacy/inefficacy, major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources). Stopping the trial at one site will result from failure to recruit at that site, or through loss of exercise resources.

STATISTICS

Methods

Characteristics of participants and practices will be compared descriptively at baseline. Comparisons between treatment arms will be made using random effects models to allow for clustering between practices. Linear regression models will be used for continuous outcome variables, logistic models for binary outcome variables, ordinal logistic regression for ordinal variables, and Poisson or negative binomial models for data on rate of falls. The assumptions for using each model will be checked and

analyses adjusted accordingly. All analyses will be undertaken, adjusted (a) for variables used for minimisation (centre, deprivation and practice size), (b) for baseline values of the outcome measure, and (c) baseline variables which differ to a clinically significant extent between groups. Differential effects of the intervention by age, sex and baseline activity levels will be assessed for the primary outcome measures by adding terms for the interaction between age, sex and baseline activity levels and treatment arm to the regression models.

Proposed Economic Analysis

The analysis will adopt standard techniques of economic appraisal (Drummond 2005). The resources used in the delivery of the interventions will be collected from records kept by PSI instructors (FaME) and the research associate and peer mentors (OEP). The use of facilities and equipment, and the time spent on travel and instruction will be included and monetary costs will be assigned according to market rates.

In addition, the use of health and social care services (GP, community, outpatient, hospital admission) will be collected for participants in all groups. Self reported service utilisation will be verified from GP records. Costs of services will be obtained from local and national sources (Curtis and Netten, 2008). Health and social care costs in the exercise groups will be compared with each other and with the usual care (no exercise) group to assess the extent to which the costs of the exercise intervention may be offset by savings elsewhere in the health and social care system.

The main outcome measure for the economic analysis will be quality adjusted life years (QALYs) using SF-12 scores transformed into EQ-5D utility weights (Gray et al 2006). The measure of effectiveness will be mean differences in QALY scores at the end of follow up after adjustment for baseline will be estimated in an analysis of covariance. If statistically significant differences between groups are found, incremental cost effectiveness ratios will be calculated to show the extra cost incurred per QALY gained. Comparisons will be conducted between the usual care (no exercise) group and each type of exercise programme, and between the two interventions, using group means of QALY changes and costs. Bootstrap methods will be used to represent uncertainty of estimates, either for constructing confidence intervals or probability curves. Secondary cost-effectiveness analyses will be conducted using physical activity and other outcomes as the measures of effectiveness.

Sensitivity analyses will investigate the cost-effectiveness of the interventions for people with different levels of physical activity, health status and health related quality of life at baseline. The impact of uncertainties in the estimation of costs and outcome variables will also be explored using one way and probabilistic sensitivity analysis.

Sample size and justification

Sample size estimates are based on the numbers of participants needed to detect differences in proportions of participants in intervention and control groups:
1) Participating in physical activity. (Participation in physical activity is defined as reaching the national target recommendations of five sessions of 30 minutes or more (or at least 150 minutes) of at least moderate activity per week).
2) Perceived health as measured by the EQ-5D index (EuroQol Group 1990), from which mean QALY scores and the incremental cost-effectiveness ratio will be calculated.

Under individual randomisation, sample size calculations for a small effect size (0.3) (Lipsey 1993) equivalent to a mean difference of 0.05 in the EQ-5D index in general community samples requires 176 patients per study group (Rosett 1999). Published evidence of participants in a cluster randomised trial of physical activity promotion showed the proportions of participants achieving the same recommended targets for physical activity to be 14.6% (intervention subjects) vs. 4.9% (control subjects) (Elley 2003). A total of 215 patients in each study group are required to detect this difference between study groups with (90% power, 5% 2-sided significance).

Data from 24 general practices in the British Regional Heart study suggested that an intra-class correlation coefficient (ICC) not exceeding 0.02 was appropriate for physical activity outcomes among middle aged men, but this study aimed to represent the full range of cardiovascular disease prevalence across Britain and the range would probably be less in the proposed study as it is less geographically dispersed (Morris 2001). Also ICCs collected for a range of variables in primary care settings have typically averaged 0.01 (Adams 2004).

Based on an intra class correlation coefficient of 0.01 the design effect would be 1.31. If 215 participants per arm are required (before allowing for attrition) for an individually randomised design (90% power, 5% 2-sided significance), 282 per arm would be required for the clustered design. Allowing for 30% attrition, this equates to 403 per arm. The sample size is based on detecting differences between each intervention (exercise programme) and the control arm, and there is unlikely to be enough power to detect modest differences in outcome between the two intervention arms.

Assuming an average practice size of 6000 patients, 15% (900) of whom are aged 65 and over (Office for National Statistics) and a random 1 in 2 sample (ratio will vary according to the practice size) of patients are approached to take part in the study, 450 patients aged 65 and over would be approached. Assuming a minimum of 10% of these patients agree to participate (approximately 45 per practice), and allowing for an attrition rate of 30%, outcome data would be obtained on 32 participants per practice.

It is expected that all or most patients per practice will be invited to the trial. In larger than average practices, however where the patient list is very large, a 1:2 random sample of patients will be drawn. Response rates from each practice will be recorded. See the diagram 1 below for the flowchart as advised by the CONSORT statement.

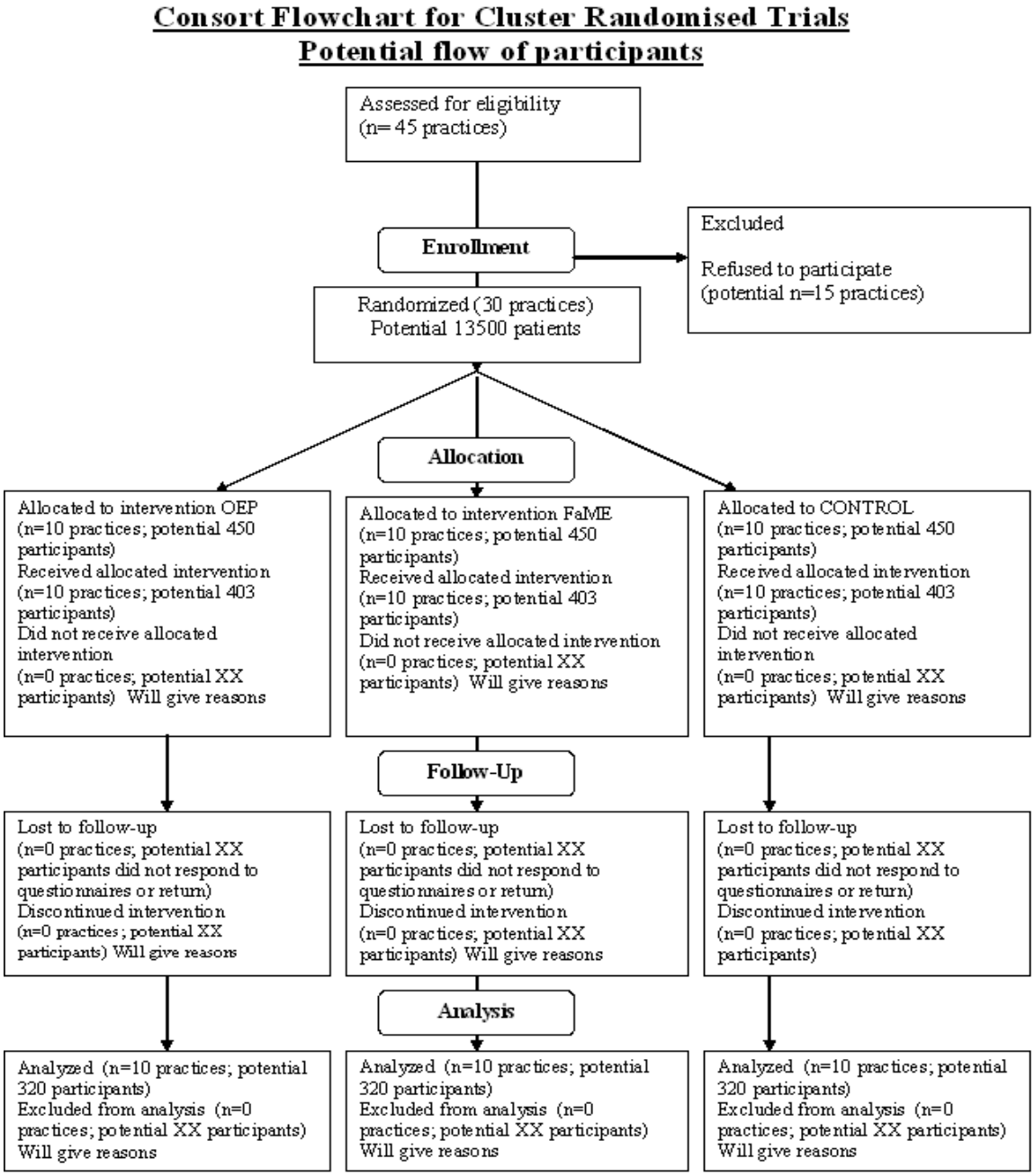

Diagram 1: ProAct65+ CONSORT Flowchart

Assessment of effectiveness

Primary outcome will be:
Proportions reaching the recommended physical activity (PA) target of at least 30 minutes of activity of moderate intensity on at least 5 days each will be measured using the CHAMPS, PASE and Phone_FITT questionnaires.

Secondary outcomes will include:

1. The direct health benefits i.e. functional and psychological status; the rate of falls and the number and nature of falls, and fear of falling.
2. Stage of change, self efficacy for exercise and physical self-perception (self-esteem relative to the physical domain), which includes measurement of perceived importance (the degree to which participants value their physical condition, body image and physical strength) to inform predictors of exercise adherence and continuation, and participants' judgement of the value or importance of physical activity.

3. Quality adjusted life years (QALYs) using SF-12 scores transformed into EQ-5D utility weights (Gray et al, 2006).
4. The NHS and private (participant) costs of each exercise programme, and possible cost offsets, identified from a comparison of health and social service utilisation of participants in all groups during the study period.

Ascertainment of outcomes Assessments will include functional assessments and validated tools to assess function, strength, balance, endurance, falls risk, fear of falling, quality of life, physical activity, self-efficacy, stages of change and physical self-perception. See appendix 6 for the methods of data collection and the timings.

We will use the following functional assessments:

1. Modified Clinical Romberg Static Balance test, eyes open and closed (Freeman 1965).
2. Timed get-up and go (with and without distraction) (TUG) as a measure of balance and falls risk (Podsiadlo 1991).
3. Functional Reach as a measure of balance and falls risk (Duncan 1990).
4. 30 second chair rise as a measure of lower limb strength and power (Rikli 1999).

We will use the following validated tools:

1. Confidence in balance measured by the ConfBal scale (Simpson 1998). A total score is provided as a measure of confidence.
2. Confidence in carrying out a range of basic activities of daily living without falling measured by the Falls Efficacy Scale-International (FES-I) (Yardley 2005). A total score is provided as a measure of confidence.
3. Readiness to change measured by the transtheoretical model (Prochaska 1983) and applying it to exercise behaviour to determine perceived barriers (Clarke 1997) and self efficacy for exercise (Marcus 1992).
6. Quality of life: We will also use a new measure of broader quality of life in older age, developed and tested by Ann Bowling using her ESRC funded quality of life survey, and which is being used in the next phases of the Department of Health evaluation Partnership for Older People. Gold standard techniques were used to develop the conceptual framework for the Older People's QoL Questionnaire (OPQOL) and to test its psychometric properties (Bowling 2007). The questionnaire was derived directly from older people's views about what gave their lives quality, and what took quality away (Bowling et al. 2002, 2003; Bowling and Gabriel 2004; Gabriel and Bowling 2004). Respondents were participants in a national survey of the quality of life of people aged 65+, with a qualitative follow-up component.
7. Social network size and density will be measured using the brief Lubben Social Network scale (Lubben 2006). Perceived social support measured by the Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet 1988).
8. Subjective Habitual Physical Activity will be assessed using a number of validated questionnaires as this is essentially one of the main outcome measures for this trial. The reason for using more than one is to ensure all domains of activity and sport are considered and to use differing methods of recall and response to ensure we have truly captured any activity the individual does. Phone-FITT (completed over the telephone), PASE (interview led and self completed questionnaire) and CHAMPS (questionnaire completed alone) have been shown to be valid and reliable for older adults (Gill DP 2008 JAPA, Harada et al 2001, Stewart et al 2001, Washburn et al 1993), but they do have differing advantages and disadvantages (e.g. length, domain specificity). There will also be a short set of questions used in the Household Survey (Current level of activity) to see if this very brief set of questions might be useful in implementing the recommendations after the trial is complete.
9. Attitudes and beliefs about falls prevention interventions will be measured using the validated AFRIS questionnaire (Yardley et al. 2007).
10. Falls risk measured by the Falls Risk Assessment Tool (FRAT) (Nandy 2004). High risk patients will be those scoring 3 or more on the FRAT, and taking over 15 seconds to perform the TUG test (Podsiadlo 1991, Shumway-Cook 2000, Whitney 2005).

11. Self perceived health will be measured by the SF-12 (Ware 1996). SF-12 scores will be converted to EQ-5D (EuroQol Group 1990) utility weights in order to calculate quality adjusted life year (QALY) gains (Gray et al, 2006).

In addition, demographic information, habitual activity, co-morbidity, medication, use of general practice and hospital and community social services will also be recorded at baseline. The falls diaries are returned every four weeks by post and the research associates will follow-up non-responders to maximise response rate. If participants fall, RAs will call them to document the type of fall and any injury and health care usage that resulted from it. Diaries will also be used to collect records of exercise and use of health and social services from participants in all groups. Information on health service utilisation will be collected from the GP notes of consenting patients after the follow-up period and used to validate self report data.

Patient feedback will be sought from all exercise participants using a questionnaire which will include open questions pertaining to their views of the programme, reasons for drop-out, barriers to attendance and self perceptions of the benefits and disadvantages of the programmes to aid future implementation.

Follow up assessments occur at 24 weeks post commencement of the intervention, and at 6, 12, 18 and 24 months post completion of the intervention for intervention arm participants and at 24 weeks post randomisation and at 6, 12, 18 and 24 months post completion of the 24 week assessment in the control arm.

The 24 week assessment will be identical to the baseline assessment. Assessments at 6, 12, 18 and 24 months post completion of the intervention or post completion of the 24 week assessment in the control arm will comprise postal administration of the questionnaires described above.

Assessment of safety

Falls are our major safety endpoint; assessment of falls is described under the assessment of effectiveness.

Safety assessment of setting for group exercise in the FaME arm of the study will be undertaken using a safety checklist (Appendix 1).

Safety assessments of individual patients at baseline will include functional assessments and validated tools to assess function, strength, balance, endurance, falls risk, as described above.

Risk management processes are summarised in the risk management flow chart (Appendix 4) and incidents and significant adverse events will be documented and reported to site PIs, the CI and the TSC (Appendices 2 and 3).

Procedures for missing, unused and spurious data

If outcome data are missing, we will assume they are “missing at random” (MAR). This means that the probability of missing data can be predicted by variables measured at baseline. In this case, an analysis which adjusts for the baseline predictors of missingness (at least baseline response and treatment) will give an unbiased estimated of the treatment effect, making multiple imputation unnecessary. Multiple imputation will be used only if important baseline predictors are missing. Methods will then be employed which take account of the clustered nature of the data (http://www.lshtm.ac.uk/msu/missingdata/papers/newsletterdec04.pdf)

Definition of populations analysed

The full analysis set will comprise all randomised participants on whom one post-baseline assessment of the primary outcome measure is available.

The per-protocol set will comprise all randomised participants who are deemed to have no protocol violations.

The safety set will be all randomised participants who undertake at least one OEP session or FaME class.

Protocol violations

Participants who are randomised to the OEP or FaME programmes who do not undertake any of the OEP programme or attend any FaME classes will be deemed to be protocol violations.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the trial.

An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after intervention even though it may have been present prior to the start of the trial.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the trial that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the OEP or FaME programmes or usual treatment that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation for non elective procedures

4. Sudden or rapidly progressive major disablement

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other treatments, chemicals or disease provide a plausible explanation**.** This will be counted as “unrelated” for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other treatments, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other treatments, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the trial site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study treatment is not the cause. The Chief Investigator shall be informed immediately of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners.

All treatment related serious adverse events will be recorded and reported to the REC as part of the annual reports. Unexpected serious adverse events will be reported within the timeframes to the REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

Risk management

Patients will complete a health questionnaire at recruitment which is sent to their GP to confirm exclusion criteria outlined previously, prior to the commencement of either exercise programme. Previous evaluation of the OEP showed significant reductions in falls and injuries despite strict compliance with the exercise programme being only 43% (Robertson 2001) and where support was only by telephone monitoring. Compliance is likely to increase with the support of the mentors. The FaME programme showed better compliance at 66% (Skelton 2002). No adverse effects occurred in previous evaluations of both programmes and the PSIs are trained in first aid and CPR. If safe exercise guidelines are followed and there is adequate pre-exercise assessment and cautious progression of exercise intensity and difficulty the risk of injury is minimal. Prior medical assessment is only necessary in people with certain acute or chronic medical conditions (Haskell 1996) and these are part of the exclusion criteria. *"Sedentariness appears a far more dangerous condition than physical activity in the very old"* (ACSM 1998). Nevertheless we will inform all participants and their general practitioners of the potential risk of injury from any exercise programme in the information documents provided for participants and practices, so that consent is obtained with full knowledge of such risks. The clinical leads at each site (SI & DK) will liase with general practitioners engaged in the project about any individual who may have sustained an injury in the course of the trial, to facilitate any care needed.

The risk management procedures for the trial are shown in the flow chart (Appendix 4).

Trial Intervention Related SAEs

A serious adverse event that is deemed directly related to or suspected to be related to the trial intervention shall be reported to the ethics committee. The reporting form for SAEs is shown in the appendix 4.

The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the sponsor of such action.
- If the event is deemed related to the trial treatment, shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event.
- Within a further 8 days send any follow-up information and reports to the REC.
- Make any amendments as required to the trial protocol and inform the REC as required.

Participant removal from the ProAct65+ trial due to adverse events

Any participant who experiences an adverse event may be withdrawn from the trial by the Investigator if there are grounds for thinking that their health is at risk if they continue.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant and GP information sheets (if appropriate) have been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and GCP and any other regulatory requirements that might be introduced. The researcher and the participant or other legally authorised representative shall both sign and date the Informed Consent Form before the participant can participate in the trial.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The research associate shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The research associate will inform the participant of any relevant information that becomes available during the course of the trial, and will discuss with them, whether they wish to continue with the trial. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the trial, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Case Report Forms

Each participant will be assigned a unique Participant Trial Number, allocated at randomisation, for use on CRFs, other trial documents and the electronic database. CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate Trial Recruitment Log (TRL) to record confidential participant information including, name, date of birth, local hospital number or NHS number, and Participant Trial Number. This permits identification of all participants enrolled in the trial, in case additional follow-up is required.
CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.
The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, and inspection by the sponsor [UCL] and relevant regulatory authorities, including the R&D departments.

DATA PROTECTION

All trial staff and investigators will protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (the trial sponsor and funder). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated computer. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data in the London site will be backed up to both local and remote media; on the trial network drive every 48 hours to tape and on the university network drive every 24 hours to a hard drive. In the Nottingham site, electronic data stored on the university network are backed up every 24 hours.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are

no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

University College London has taken out an insurance policy to provide indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.
The trial coordinator, or where required, a nominated designee of the sponsor or funder, shall carry out a site systems audit at least yearly and an audit report shall be made to the TSC.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The trial coordinator, or where required, a nominated designee of the sponsor or funder, shall carry out monitoring of trial data as an ongoing activity.

Adherence to exclusion criteria will be checked by review of the patient health questionnaires and the GP exclusion checklist. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING
In compliance with the ICH/GCP guidelines, regulations and in accordance with the University College London and University of Nottingham Research Codes of Conduct, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least seven years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.
The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at UCL. This archive shall include all trial databases and associated meta-data encryption codes.

STATEMENT OF CONFIDENTIALITY
Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.
Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the UCL and University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Our dissemination strategy, assuming that we can demonstrate evidence of benefit from the interventions, will use multiple methods and media to reach our main target audiences, namely:
1. Primary care commissioners, who will need to know that the effective intervention can be implemented in their health economies.
2. Primary care practitioners, who will need to know what benefits from exercise could be anticipated by which patients, and what risks of exercise need to be considered.
3. Voluntary sector organisations and the leisure industry, both of which will need to know how they can work closely and in partnership with each other and with commissioners in the configuration of services.

All investigators will contribute towards drafting the paper reporting the main trial findings and all investigators will be named authors on that paper, providing they fulfil the Vancouver criteria for authorship.

Investigators wishing to analyse and report other findings from the study can do so on the agreement of the other investigators, and the study team will agree authorship for these papers, subject to the Vancouver criteria for authorship.

All publications will be submitted to the HTA for information only, 28 days prior to publication.

USER AND PUBLIC INVOLVEMENT

User representatives will be involved in the development, implementation and interpretation of the study. This involvement will include: advice on recruiting patients, invitation letters, the design of information leaflets, and research instruments, piloting assessments, helping to assess progress, and contributing to the evaluation of the project, the interpretation of findings and the dissemination of results. User representatives will be invited to trial steering committee meetings and also provide assistance in each centre. The Nottingham centre has established links with the research advisors (consumers) from the Nottingham Primary Care Research Partnership. The Chief Investigator has good working relationships with the voluntary sector, particularly through Age Concern, and with Better Government for Older People.

TRIAL FINANCES

Funding source

This trial is funded by the HTA (project code 06/36/04).

Participant stipends and payments

Participants will not be paid to participate in the trial. Travel expenses will be offered for any hospital visits in excess of usual care.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Co- investigator: (name) _____

Signature: _____

Date: _____

Trial Statistician: (name) _____

Signature: _____

Date: _____

Trial Statistician: (name) _____

Signature: _____

Date: _____

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APPENDICES

1. ProAct65+ Risk Assessment and Management Tool: PSI Safety Checklist

2. ProAct65+ Risk Assessment and Management Tool: Incident report form

3. ProAct65+ Risk Assessment and Management Tool: Serious Adverse Event Reporting Form

4. ProAct65+ Risk Assessment and Management Tool: Risk Management Pathway

5. ProAct65+ Timetable

6. ProAct65+ Instruments: Methods of Collection and Timings

Appendix 1 ProAct65+
Risk Assessment and Management Tool
PSI Safety Checklist

Venue:
Date:
Time:
Group ID:

Nearest Hospital Casualty Department Telephone Number:

	Please tick the box below if the answer is yes and put a cross if the item has required remedial action	Please write comments clearly and legible with regard to any steps taken to ensure Health and Safety at the venue
Fire Exits accessible		
Heating/Ventilation acceptable		
Toilets/Refreshments acceptable		
Areas free of Hazards e.g. columns, furniture, access to and from exercise area and toilets etc		
First Aid Kit accessible and portable		
First aider identified		

Emergency Telephone accessible		
Areas free of any loose Electrical Cables, Wires etc		
Additional seasonal safety precautions in place and taken as appropriate e.g. water and extra seats in heat, anti-slip mats in rain, extra assistant in bad weather		
Transition to and from transport is safe and adequately staffed		
Protocol in place in event of accident, illness, and is regularly rehearsed		
Copy of any accident/illness incident is copied to trial staff		
Emergency Contact Telephone Numbers available		
Signed and dated by PSI		

Please complete this form at the first FaME exercise session for each exercise group at a venue and return it, signed and dated to the research office:

Miss Zoe Stevens
Primary Care and Population Health
Royal Free and University College Medical School
Hampstead Campus
Rowland Hill Street
London
NW3 2PF.

Appendix 2 ProAct65+ Risk Assessment and Management Tool

ProAct65+ Incident Report Form

Participant Name : **Place of Incident :**

Practice code : **Person taking report [Name and Job Title] :**

Date of Incident :

Details of the Incident **Action Taken** **Witness Name and Comments**	
Outcome	
PSI, Peer mentor or Research staff Name: …… **Signature:……..** **Date: ……...**	**Witness Name: ……** **Signature: ……..** **Date: ……**

London Research Site Contacts	
Chief Investigator; Dr Steve Iliffe Phone: 0207 830 2393	**Research Associate; Ms Cate Barlow: 020 7794 0500 ext……**

Appendix 3 ProAct65+ Risk Assessment and Management Tool

Serious Adverse Event Reporting Form

Patient ID: _ _ _ **Patient Initials:** _ _ _

Patient Date of Birth: _ _/_ _/_ _ **Allocation Group: FaME/OEP/Control**

Date form completed: _ _/_ _/_ _

Death (any cause): Yes ☐ No ☐
Description: _____
_____

Date of occurrence _ _/_ _/_ _

Hospital Admission: Yes ☐ No ☐
Description: _____
_____
Was the admission as a result of a fall? Yes ☐ No ☐

Injurious fall without Admission: Yes ☐ No ☐
Description: _____
_____
_____

Fall During the exercise sessions:

Did a fall or medical event occur during an actual exercise session, requiring medical attention? Yes ☐ No ☐

Form completed by:
_____ (Print name) Date_ _/_ _/_ _____ (Signature)

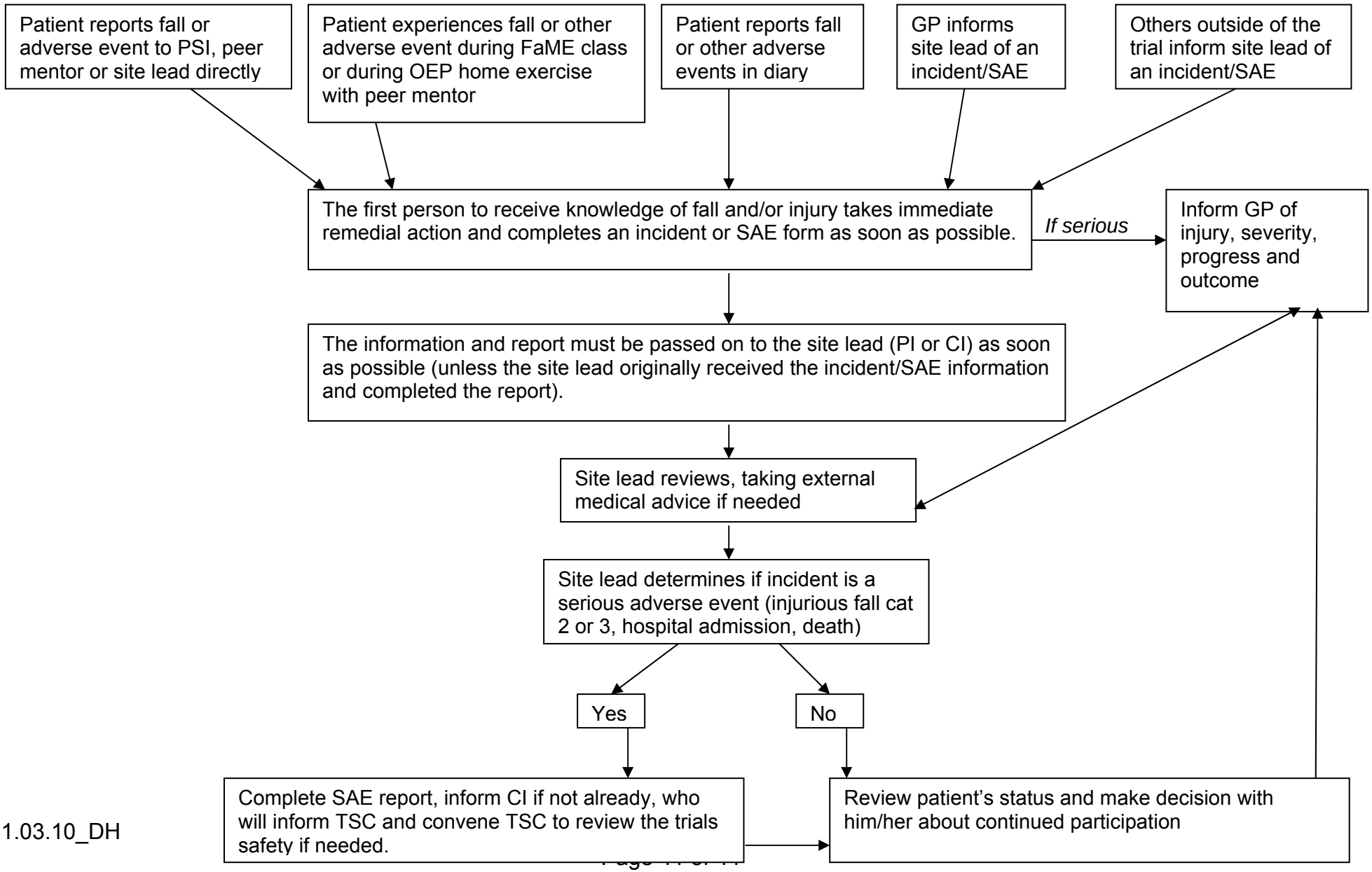
Form reviewed by
_____ (Print name) Date_ _/_ _/_ _ _____ (Signature)

For Chief Investigator
Is this event an SAE relating to patient safety in the trial?
☐ Yes – inform TSC, convene meeting to discuss trial safety
☐ No – no further action required

Signed by Chair of TSC **Date**

London Research Site Contacts	
Chief Investigator; Dr Steve Iliffe Phone: 0207 830 2393	**Research Associate; Ms Cate Barlow: 0207 794 0500 ext…….**

Appendix 4 ProAct65+ Risk management pathway



Appendix 5 ProAct65+ Timetable

Timetable			Action
Year	Month	Date	
1	**1**	**June 2008**	**Trial Management Group (TMG) meeting**
1	1 - 4	June - Sept 2008	Apply for ethical and R&D approval. Recruit user representatives (URs) in both centres. Recruit clerical support staff in London and Nottingham/Derby (SI/DK/Trial manager).
Target	1	June 2008	Employment of clerical staff (CS). Purchase of computers, printers and software. Recruitment of user representatives in both centres.
Target	3	August 2008	Obtain ethical and R&D approval.
1	4 - 12	Sept 2008 - Jan 2009	**First Trial Steering Committee (TSC) and Trial Management Group (TMG) meeting** Recruit research associates in London and Nottingham/Derby (SI/DK/Trial manager). Approach general practices through the Primary Care Research Networks (PCRN) in London and Nottingham / Derby (SI/DK/TM). Recruit general practices (SI/DK/TM). Brief practice staff in participating practices on the details of the study, the assessments, exercise programmes and recruitment of patients (SI/DK/Trial manager). Identify random lists of patients to target for recruitment (Trial manager/DK with practices). Production of invitation letters and research questionnaires (Trial manager/DK/CS). Piloting of invitation letters, study information leaflets, and research questionnaires (SI/ Trial manager/DK/URs). Allocation of practices to study arms (FaME, OEP, Usual care) (Trial manager/DK/RM). Obtain Research Governance. Development of databases for entry of research data (Trial manager) Identify class venues.
1	9 - 12	Feb - May 2009	Training of peer mentors (BL). Train research assistants to deliver the OEP home exercises, the FRAT and the functional assessments (SD/DS). Quality assurance training of PSIs (SD) and organisation of community venues for exercise classes (DS/SD/ Trial manager). Recruit PSIs and plan quality assurance training timetable (SD/DS). Recruit peer mentors and train peer mentors (SD/DS).
1	**4** **6** **7**	**Sept 2008** **Nov 2008** **Dec 2009**	**TMG meetings**
Target	7	Dec 2008	Employment of research associates (RAs)
Target	11	April 2009	First mailing of invitation letters to invite patients to participate (CS). Subsequent scheduling of appointments for baseline assessments
2	13 - 24	June 2009 - May 2010	Patient recruitment - baseline assessments and interventions begin.

			Continuation of FaME and OEP.
2	**13**	**June 2009**	**Second TSC meeting**
2	14 - 23	July 2009 - March 2010	First baseline assessments (RAs) (staggered over months 14 to 23 inclusive). To consist of interview and include functional assessments, administration of research questionnaires and fall diaries. Introduction of home exercise to OEP participants. Ongoing data entry of research questionnaires and data cleaning (RAs/CS/Trial manager)
Target	15	Aug 2009	Enrolment into FaME exercise classes, (maximum of 15 participants per class). OEP participants to start home exercise programme.
2	**16 19 22**	**Sept 2008 Dec 2008 March 2009**	**TMG meetings**
2 - 3	21 - 30	Feb 2010 - Nov 2010	24 week assessments (RAs) (staggered over months 21 to 30 inclusive). Same assessments as at baseline.
3 - 5	25 - 53	June 2010 - Oct 2012	Follow-up period
3 and 4	**25 and 37**	**June 2010 and June 2011**	**Third and fourth TSC meeting**
3	27 - 36	August 2010 - May 2011	6 month assessment (mailing of research questionnaires) (CS)
3	**28 31 34**	**Sept 2010 Dec 2010 March 2011**	**TMG meetings**
3 - 4	33 - 42	Feb 2011 - Nov 2011	12 month assessment (RAs) (staggered over months 28 to 38 inclusive). Same assessments as at baseline.
4	39 - 48	Aug 2011 - May 2012	18 month assessment (mailing of research questionnaires) (RAs/CS)
4	**40 43 46**	**Sept 2011 Dec 2011 March 2012**	**TMG meetings**
4 - 5	45 - 54	Feb 2012 - Nov 2012	24 month assessment (mailing of research questionnaires) (RAs/CS)
5	**49**	**June 2012**	**Fifth TSC meeting**
5	**52 55 58**	**Sept 2012 Dec 2012 March 2013**	**TMG meetings**
Target	54	Nov 2012	Start collection of data from patient records for economic analyses (RAs)
5	55 - 60	December 2012 - May 2013	Data cleaning, Statistical and Economic analysis Write-up and draft report and draft paper for peer reviewed journal

End of the Trial

Appendix 6 ProAct65+ Instruments: Methods of Collection and Timings

Method	Variable	Base-line	Intervent-ion (24wks)	Post intervention			
				6 month	12 month	18 month	24 month
Face to face by research associate	Patient health (BMI, BP, pulse, diagnosis, general health, activity level)	√	Some				
	Demography (age, gender, ethnic, living arrangements, education, income)	√	Some				
	FRAT	√	√				
	Functional tests (timed up and go, functional reach, balance, chair stand, 6 minute walk)	√	√				
	Previous month service use	√					
	Cost of attending FaME		√				
	SF – 12/QALYs	√	√				
Self completion	SF-12/QALYs			√	√	√	√
	PASE	√	√	√	√	√	√
	Balance	√	√	√	√	√	√
	Falls self efficacy	√	√	√	√	√	√
	Exercise expectations	√	√	√	√	√	√
	OP QoL	√	√	√	√	√	√
	Social support sources	√	√	√	√	√	√
	Lubben relatives/friends	√	√	√	√	√	√
	CHAMPS	√	√	√	√	√	√
	4-week diary: falls, exercise, service use	Throughout the whole trial					
Research associate by phone	PhoneFITT	√	√	√	√	√	√
	AFRIS	√					