KEY DOCUMENT REVIEW / APPROVAL

Trial:	**PREFIT**		
Chief Investigator:	**Professor Sarah Lamb**		
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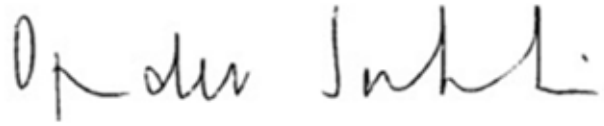
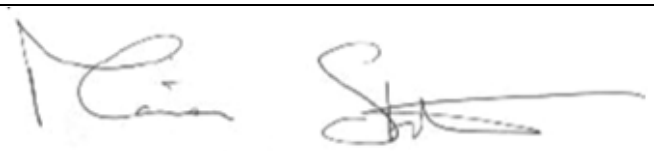
Reviewers: By signing this form, you confirm the content of the document found to be correct.			
Name	**Role in trial**	**Signature**	**Date**
Professor Stephen Walters	*DMC Chair Member*		18/05/2018
Professor Opinder Sahota	*DMC Member*		29/05/2018
Professor Maria Stokes	*DMC Member*		24/05/2018

Summary of changes

1. Clarification on the events to be counted as fractures
2. Final update on fracture inclusion, now expanded to include ribs, sternum, facial, cranial and some types of vertebral fractures.
   Selection of fractures to be reported separately
   Definition of fracture dates
   Definition of fracture episodes
   Fractures over a longer time period
   Addition of SAP disclaimer
   Final definitions of compliance
3. Rules for hierarchy of tests revised to ensure consistency with the contract from the funder and original protocol.

STATISTICAL ANALYSIS

PLAN FOR THE PREFIT TRIAL

CONTENTS

2. AIM AND DESIGN OF THE PreFIT TRIAL

This section outlines the study design for the PreFIT trial.

2.1 Objectives

The aim of the PreFIT trial is to estimate the comparative effectiveness and relative cost-effectiveness of three primary care fall prevention interventions.

The trial will contribute a substantial body of evidence to inform UK healthcare practitioners, commissioners and other stakeholders on the relative effectiveness and cost effectiveness of a range of primary care options for preventing falls and fractures.

2.2 Study Design and interventions

- A pragmatic, multi-centre cluster randomised controlled trial.
- Unit of randomisation is the general practice.
- The study will investigate a primary prevention screening strategy investigating the effectiveness and cost-effectiveness of three alternate interventions (advice, exercise, multifactorial falls prevention programme (MFFP)).
- This is a superiority trial which will recruit a minimum of 9,000 community dwelling people aged 70 years and older.

2,3 Eligibility criteria

2.3.1 General practice inclusion criteria

General practices will be eligible to participate in the trial if they meet all of the following criteria:

- Located in the region that has the infrastructure to provide the active interventions;
- Technical capability for electronic searching, extracting and reporting of aggregated and individual-level data;
- Agree to adhere to a randomly allocated intervention and to support research staff in the execution of the research protocol.

2.3.2 Participant inclusion criteria

Participants will be eligible to participate in the study if they meet all of the following criteria:

- Provided a signed informed consent form;
- Aged 70 years or over ;
- Live in the community, including living in sheltered or supported accommodation.

2.3.3 Participant exclusion criteria

- Participant will not be eligible to participate in the trial, if they meet any of the following criteria:
- Live in residential care or nursing home;
- Limited life expectancy (< 6 months) as determined by GP.

2.4 Randomisation

- Unit of randomisation is the general practice.
- The Warwick Clinical Trials Unit programming team will generate the randomisation. The clusters are allocated to the interventions by the data management team
- General practices will be randomly allocated in blocks of three with one of the three trial treatments. There is no stratification and the method of randomisation is minimisation by general practice.
- Practices will be randomised simultaneously when the initial record searches have been completed and the sample identified and enrolled (400 participants screened and contacted to obtain a sample of 150 enrolled trial participants) at all three practices in each block.

2.5 Blinding

- It is not possible to blind participants to the treatments they are receiving or to blind the health care professionals delivering the interventions. Participants were 'blinded' to the alternative treatment options.
- Researchers responsible for data entry and analysis will be blinded to the allocation.

- In addition assessment of the primary outcome will be blinded when data are drawn out of HES and data on 'suspected' fracture events will be validated by researchers who are blind to the cluster allocation.

2.6 Outcome measures

Primary outcome

The primary outcome is fractures expressed as the fracture rate per person per time unit observation over 18 months.

Fracture data are collected from three sources as described in Bruce et al 2016 (Appendix 1). In summary, we will use a process of searching across three sources (self-report, GP record and HES). Fractures will be those in which there is a confirmed report either in the HES data or GP record. A report in HES or the GP record will be confirmatory with or without a self-report. In addition to confirmed fractures we will provide data on all fractures meeting the definition below regardless of the source of reporting. Adjudication of fracture events will be undertaken by two clinically qualified members of the study team (SL/MU) with experience in fracture management. Where needed, further adjudication will be made by KW.

We will include:
All fractures of the peripheral (appendicular) skeleton in accordance with the PROFANE network consensus (Lamb 2005). Fractures of the skull, ribs and face and vertebral column.

We will exclude:
Vertebral compression fractures which cannot be attributed to a fall.

Clarification of changes in events being counted in the primary outcome.

The definition of included events has evolved since the original protocol and published protocol (BMJ Open, 2016) for the following reasons. There is broad recognition that the

PROFANE consensus which was published in 2005 needs to be updated to reflect the contemporary epidemiology of trauma related fractures in older people (Copsey et al 2016). As populations are ageing, the prevalence of trauma related skull, rib, vertebral and facial fractures is increasing (Kannus et al 2007, Palvanen et al 204, Amin et al 2014, Korhonen et al 2014, Kannus et al 2016). These fractures are no longer negligible in number.

As we have developed methods for extracting data from both Hospital Episode Statistics and GP records it is apparent that reporting is sufficient to be able to distinguish fall related versus non-fall related compression fractures of the vertebral column. We will include vertebral fractures from HES and GP records where these are consistent with a trauma mechanism (there is a clear description of trauma/fall or the fracture presentation is consistent with trauma and maps to the ICD-10 codes being generated from HES as detailed in Appendix 1). Reports of vertebral osteoporotic compression fractures in GP records will be excluded unless clearly linked to a report of trauma/fall.

All fractures that are ascertained in GP record searches will be assigned a code and data similar to the coding framework and definitions used in ICD 10 2010 version, and as outlined in Appendix 1. The search strategy used for GP READ code searching is provided in Appendix 3/available from study team.

We have updated the list of fractures to include the face and cranium as reported in Bruce et al (2016). We will also include rib fractures as these were omitted from the published protocol.

Secondary outcomes

Secondary outcomes will encompass the following:

- *Fracture rate per person month of observation for the entire available period of observation*

We have collected additional data on fractures from HES for a time period that extends beyond 18 months after randomisation. This data will also be summarised and analysed.

- *Proportion of people sustaining one or more fracture over 18 months*

- *Time to first fracture*

  We will attempt to date all fractures. The date of fracture will be taken as the A&E attendance or HES episode admission date where these exist. In addition, we will check GP records for confirmation of fracture dates where these are recorded, with the exact date of fracture event if reported taking precedence over HES and A&E attendance if these differ.

- *Fracture episodes*

  It is possible that people will experience multiple fractures from one fall. It will not be possible to consistently attribute fractures to a single fall event. Instead we will estimate fracture episodes. We will characterise all the fractures occurring on the same date as one episode. We will use statistical modelling to account for fractures occurring in the same individual and in the same episode. We will report and explore the number of episodes of fractures and recurrent fracture episodes. We may not be able to generate sufficient resolution in the data to assign fractures to episode. If so, we will not report these data (this will be apparent after the data cleaning is finalised).

- *Fracture regions*

  We will estimate the difference in number of proximal femoral fractures (hip fractures) and fractures involving the distal radius (wrist fractures). Hip fractures were defined as verified fractures with a specific description of neck of femur or proximal femur. Fractures described as subtrochanteric, femoral shaft, distal femur, or simply femoral will not be categorised as hip fractures.

- *Falls rate per person per month observation over the 18 months*

- *Proportion of people sustaining one or more fall over the 18 months*

- *mobility/ADLs:*
  Questions on difficulties balancing on a level surface, ability to walk outside of the house, and average time spent walking.

- *Frailty:*
  A 16 item frailty questionnaire. We will report sub-domains and the overall domain scores for the follow up time points in which we have these data.

- *Cognitive ability*:
  A clock-drawing test used as for cognitive screening.

- *Health related quality of life*:
  EQ-5D and SF12 sub-domain and overall scores.

- *Resource use*
  Routine Hospital Episode Statistics (HES) data and CRF data
  Unit cost data

Process variables

- Uptake of the intervention(s)
- Compliance with the intervention including medication prescriptions where available, attendance at exercise sessions, attendance at MFFP assessment.

Safety

- Serious adverse events and adverse events will be reported.

2.7 Planned sample size

The primary outcome is the fall related fracture rate, expressed as the fracture rate per person per unit time of observation over 18 months after randomisation of the General Practice.

In the UK, the annual fracture incidence per 100 men aged 55-74 years is 2.6 (95% CI 1.9 to 3.3); this rises to 7.6 fractures (95% CI 4.0 to 11.3) per 100 women aged of the same age range over 55 years (Donaldson et al, 2008).

Adjusting for differences in gender in the general population (ONS 2006) yields a fracture rate of 6 per 100 people (6%) aged over 70 years. This estimate does not account for repeat fractures within a person and hence is a conservative estimate of the fracture rate.
To have 80% power to detect, as significant (p<.05), a 2% reduction in fracture rate, from 6% to 4% (relative risk reduction, 0.67), requires 1900 participants per arm, or 5,700 overall. Incorporating a design effect to adjust for varying degrees of modest clustering (ICC range .001 to .003), inflates the sample size estimate to 7800, or 2,600 per arm. Allowing for 10% loss to follow-up, yields a target sample size of 9,000 participants. To recruit 9,000 participants at 150 per practice requires 60 general practices.

2.8 Planned subgroup analyses

We have selected sub-group criteria using simple data available in primary care. We will run confirmatory sub-group analyses on fracture outcomes for the following:

- **Age:** We will examine whether interventions are best targeted to the oldest old (<=80 years or > =81 years).
- **Gender:** There is considerable excess risk of falling and fracture in women.
- **Previous history of falls in the last 12 months:** This is not well recorded in primary care, and hence will depend on self-report;
- **Frailty**: This will be based on the categorisation of the Strawbridge questionnaire - not frail (rarely or never/sometimes) versus frail (often/very often).

- **Cognitive impairment**: If there are sufficient numbers of people scoring less than 5 on the cognitive impairment sub-test, we will run a sub-group analysis with cut-points less than 5 or 5 or more.

3. PLANNED INTERIM ANALYSIS AND THE ROLE OF THE IDMC

- A document detailing the framework of operational and statistical futility was compiled during the pilot stages. This document detailed the challenges that the trial faces in carrying out a formal futility analysis after the pilot was complete or during the main trial.
- No formal futility analysis was carried out at the end of the pilot stage.
- The responsibilities of the Independent Data Monitoring Committee (IDMC) are to monitor the data and make recommendations to the TSC on ethical or safety issues arising and to ensure the safety, rights and well-being of trial participants. The IDMC will consider the need for interim analysis and consider data emerging from other related studies. Provide information on the data obtained if requested by the Chief Investigator, TSC, Trial Sponsor or Trial Funder if further funding is required for the trial to continue.
- The IDMC will meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be feed into the TSC.
- They IDMC, TSC and funder reviewed the pilot data and considered the trial viable.

4. MONITORING OF THE TRIAL

Monitoring of the trial is a continual process, from the start to the end of the study. At the end of the trial two aspects related to monitoring will be examined:

(a) Operational (logistical) and Process Management monitoring from top level down (i.e. region, general practice and participant level);

(b) Monitoring – recruitment, retention and uptake of the intervention.

4.1 Operational (logistical) and Trial Management of Regions

- There are 5 *regions* recruiting participants to the PRE-Fit trial: Devon, Warwickshire / Herefordshire, Worcestershire, Cambridge and Newcastle.

- Within the regions are the general practices. These general practices are randomised in clusters of 3, and within each general practice all participants are allocated to the randomised intervention.

4.2 Operational (logistical) and Trial Management monitoring of General Practices

Number and size of general practices and its impact on the Sample Size

- The primary outcome is fractures, expressed as the fracture rate per person unit time of observation.
- The unit of randomisation is general practice. It is likely that the primary outcome may not necessarily be distributed in the same way across all the general practices – some general practices may be more likely to have a greater rate of fractures and others less. To allow for the different degrees of 'clustering' of fracture rates across the general practices, we compute the intra cluster correlation (ICC) coefficient.

- The sample size is based on the proportion of participants having at least one fracture. This would suggest that to assess the ICC, for a given participant, we have a binomial distribution of a facture (1) or no fracture (0) and we using methods stated by Chakraborty et al, 2009. Proc GLIMMIX (using link=logit distribution=binomial) will be used to estimate the ICC.
- The parameters which are required to obtain the (ICC) will be summarised. These include the number of general practices, the number of participants within each general practice, the number of participants with at least one fracture (primary outcome) within each general practice, the number of fractures. These parameters will be used to obtain the ICC and we will assess its impact on the overall sample size.

4.3 Operational (logistical) and Trial Management monitoring of participants

The reporting of the study will follow the guidelines set by CONSORT (2001) and extension to cluster randomised trial update statement (BMJ 2012). The report will detail the design, conduct, analysis and results of the data. This report will be supported by the tables, plots and flow diagrams that have been included in a separate document and signposted here.

4.3.1 Recruitment of participants

- Participants recruited within each general practices from the GP list size to the point of randomisation.

- Participants recruited within each general practices from the point of randomisation to end of intervention.

- Participants recruited within each intervention from the GP list size to the point of randomisation.

- Participants recruited within each intervention from the randomisation to the end of the intervention.

- A recruitment graph will show the number of participants recruited in randomised GP Practices over the entire study period.

4.3.2 Intervention Phase

The flow of participants by treatment arm using the CONSORT diagram.

The number of participants in the balance screener risk categorisation by each intervention arm.

4.3.3 Treatment received

For the MFFP+ advice arm, 'treatment received' is when the participants have had an MFFP assessment. They may then be referred on for additional treatments following this assessment.

For the Exercise + advice arm, 'treatment received' is when the participants have had their first assessment.

4.3.4 Compliance/adherence

Treatment received: for the MFFP+ advice arm, 'treatment received' is when subgroups of eligible participants referred for the MFFP intervention have received their falls assessment.

We will tabulate the summary statistics of the number of participants who complied with the active interventions. Extent of "adherence" varies by intervention arm. This table will show the number of who attended 1 session, 2 sessions, 3 sessions and so on. Thus for MFFP, participants are only invited to attend one falls assessment therefore this counts as 1 session only (although with potential for onward referral for other specialist treatment but we count 1 appointment as assessment completed). For the Exercise+advice intervention arm, this is a recommended 6 month supported programme. We have start date and discharge

date for exercise on the main PreFIT database, thus can look at “exposure” by number/type of contacts.

4.3.5 Follow-up

We will tabulate number of participants that were followed-up at each of the time points (4, 8 and 12 and 18 months).

4.3.6 Violations or deviation from the protocol

- Protocol violators/deviators will fall into one of the following categories.

(i) Participants who receive an intervention different from that allocated;
(ii) Withdrawals;
(iii) Ineligible participants – any participant who was ineligible but subsequently received treatment in the randomised general practice.

5. OUTCOMES OF THE TRIAL

OUTCOMES	TIME POINT collected at	SCORING
Primary outcome		
Fall related fractures	Over the 18 months (Baseline, 4, 8, 12 and 18 months).	Fall fracture rates (per person per month observation) This will be obtained by estimating the rate over 18 months and fractioning this as a monthly rate
Secondary outcomes		
Additional fracture parameters		• Proportion (and number) of people sustaining at least one fracture over the study period will be obtained. Thus, the derived variable will be binary (patient with at least one fracture =1/ no fracture =0). • Time to first fracture • Fracture rates and proportions for data extending beyond 18 months
Falls (CRF)	Over the 18 months (Baseline, 4, 8, 12 and 18 months)	• Fall rates (per person per month observation) • Proportion (and number) of people sustaining at least one fall over the study period.
Falls (Diary)		

Analysed at 4, 8, 12 For sensitivity analyses only	Baseline, 4, 8, 12 months	• Fall rate (per person per month observation) • Proportion (number) of people sustaining at least one fall
Frailty Strawbridge Questionnaire	Baseline and 18 months	To summarise, the frailty questionnaire is Strawbridge 1998 with the four domains: physical, nutritional, cognitive and sensory. The score of this based on a 4 –point ordinal scale (rarely or never / sometimes /often /very often). We will analyse overall and sub-domain scores
Mobility	Baseline, 4, 8, 12 and 18 months	Questions on difficulty in balancing on level surface, ability to walk outside of the house and average time spent walking.
EQ-5D	Baseline, 4, 8, 12 and 18 months	Evaluates patients QOL based on 5 dimensions converted into a single summary score (range: -0.57 to 0 (death) to 1 (perfect health state)).The ED-5D will be scored using the devised algorithm (EuroQol Group, 1990) and summarised as detailed in the User Guide (EuroQol Group, 2005).
SF-12	Baseline, 4, 8, 12 and 18 months	Scoring of the SF-12 will be carried out using 'the SF-12v2- How to Score version 2 of the SF-12 Health Survey' manual (Ware et al.1996).
Predictor variables		

Clock test	Baseline	Simple scoring system used e.g. 6 point scale of Shua-Haim et al. 1996: (1) Approx. drawing of clock face; (2) Presence of numbers in sequence; (3) Correct spatial arrangement of numbers; (4) Presence of clock hands; (5) Hands showing approx correct time; (6) Hands depicting the exact time

6. STATISTICAL ASPECTS

The statistical analyses will be carried out using SAS (version 9.13).

All statistical tests will be two-sided and performed at the 5% significance level.

6.1 Analysis Populations

Two populations of interest here are:

6.1.1 Intention to treat (ITT) analysis (all patients who were recruited in the randomised GP practice regardless of falls risk)

An ITT analysis would measure something more important than intervention efficacy, namely intervention policy. That is, it tests whether it is better to screen and then *prescribe* one of the experimental interventions to those at high risk rather than providing advice only (i.e. an 'as-randomised analysis' or intention to treat (ITT) compares the outcomes of participants by assigned group). The ITT effect is the effect of treatment assignment rather than the effect of treatment taken (often called 'effectiveness' as opposed to 'efficacy'). A full 'Intention-to-treat' analysis is only possible when complete outcome data are available for all patients. One of the main reasons for advocating ITT analysis is that it gives an estimate as would be in the 'real world' and it also maintains the baseline comparability achieved by the randomisation process. If the initial random assignment is undermined, then confounding can be introduced and the internal validity of the results is consequently questionable.

The PREFIT trial consists of three intervention arms:

1) Advice only;
2) Advice, screening and exercise;
3) Advice, screening and MFFP.

Analysis will be at two levels:

a. We will compare between the advice only and exercise arm, and separately, the advice only and MFFP arm.
b. If there is evidence of a statistically or clinically important difference in either of the comparisons with advice only, we will then proceed to test exercise versus MFFP head to head, recognising that this comparison potentially has less power if both interventions were effective.

6.1.2 Nested Intention to treat

In a nested analysis we will present our finding just for those at intermediate/high risk of falling. We will establish the risk score of falling, using the baseline questions which are analogous to those on the Balance Screener but enable us to identify the at risk population across all three arms. The reason for using the baseline questionnaire is to ensure the risk score is available for all patients including those on the control arm as well as those on the interventions.

6.1.3 Allocation to the intervention (CACE analysis)

Taking the 'intermediate/high groups within each intervention arm, we will be able to establish the compliers and non-compliers.

Compliance will be defined as:
complier = Balancer screen returned and at risk of falling (i.e. categorised as high or intermediate) and had first assessment *or* balance screener returned and low risk of falling.
Non-compliers = Balancer screen returned and at risk of falling (i.e. categorised as high or intermediate) but did not have first assessment *or* no Balance screener returned (although sent)

Using these we will be able to carry out the 'complier average causal effect' (CACE) analysis. The CACE analysis is the intervention effect among the true compliers; the difference in outcome between compliers in the treatment group and those controls who would have complied with intervention had they been randomised to the treatment group.

Complier average causal effect (CACE) is a measure of the causal effect of the intervention on the patients who receive it as intended by the original group allocation. Because it retains the randomisation assignment, it overcomes the problems related to per-protocol and on-treatment analysis.

CACE analysis makes two assumptions; the first is that members of the control group have the same probability of non-compliance as members of the intervention arm. If allocation is genuinely random, this statement must be accepted as true. This second is that merely being allocated to the intervention has no effect on outcome; i.e. outcomes are the same for participants who were not treated with one of the experimental intervention in both that intervention and advice only arms. Both of these assumptions appear reasonable for this trial.

Although this analysis has been specified, it is unclear at the onset whether it will be possible to carry it out due to model restrictions/assumptions. Hence we will explore these and compute fit these models, if possible.

6.2 Analysis Datasets

The primary dataset for the analysis will be the observed dataset. The imputed dataset will be used for sensitivity analysis, if required.

6.2.1 *Observed dataset*

This will comprise of all the data observed (including follow-up) with missing values. The data will also include a variable to indicate what treatment patients were randomised to and another variable to indicate what treatment they actually received so that the 'ITT' and 'CACE' analyses can be implemented.

6.2.2 Imputed dataset (missing data)

We will assess the extent of missingness for each of the outcomes by summarising the data. If missingness is problematic, we will then compute a sensitivity analysis, namely imputation analysis, to assess the effect of the missingness.

If imputation methods are required for the primary outcome, we will explore the possibility of implementing these. However, due to distributional constraints, we may not be able to adequately model the missingness for the primary outcome.

Data can be missing in fields in two situations: (a) when it is not applicable (validly missing) and (b) it can be missing due to patient/health professional leaving fields blank when they should have completed the question with an answer (invalidly missing). The latter will be examined for the different data mechanisms (MAR - missing at random; NMAR - not missing at random; MCAR - missing completely at random) and we will assess whether multiple imputation is viable. In the case where multiple imputation can be used and the data can be assumed normal, multivariate methods will be applied. In the case where one cannot assume a distribution of the data, the ICE (imputation by chain equations) will be used.

6.3 Statistical Analysis

Comparison of those decline/excluded with those who were consented

Where possible, appropriate variables will be summarised for these to sub-population to ensure that the groups are comparable and representative of the entire population.

6.3.1 Demographic and baseline

These data will be summarised using mean, standard deviation, median and range values as appropriate. In the case of the categorical assessments, the number of patients (together with the percentage) will be specified.

6.3.2. Outcomes

6.3.2.1 Covariates to adjust in the statistical models

The covariates that will be used to adjust for in the statistical models will be corresponding baseline variable, deprivation score (for the GP practice), age and gender.

6.3.2.2 Primary outcome

Fracture rate (per person per month) observation has a skewed distribution (heavy skewed in favour of zeros). We will explore the possible models that may account for this skew: (a) Poisson model; (b) zero inflated Poisson model; (c) negative binomial; (d) zero inflated negative model.

For the fracture rate (per person per month observation), we will assess this over the 18 months, using an 'offset' variable in the appropriate model, and also incorporate the general practice variable as the random effect.

Proportion of patients having at least one fracture, will be analysed using logistic regression models, with the random effect as general practice. The adjusted analysis will incorporate the appropriate covariates (as stated above).

Time to first fracture will be assessed using survival analysis methods.

6.3.2.3. Secondary outcome: falls data

Falls data and falls rate will be summarised and statistical assessed in a similar way to the primary outcome.

6.3.2.4. Secondary outcome: Diary card data – falls data

Diary card falls data will be summarised and statistical assessed in a similar way to the primary outcome.

6.3.2.5. Secondary outcome: EQ 5D

The items of the EQ-5D will be summarised for each of the interventions and time-points.

The EQ -5D score will be summarised using mean, standard deviation, median and range values. The mean difference (and the 95% of the mean difference) between treatment arms will be reported. Both adjusted and unadjusted random effect linear regression models will be fitted to the data.

6.3.2.6. Secondary outcome: SF-12

The mental and physical components of the SF-12 will be summarised using mean, standard deviation, median and range values. The mean difference (and the 95% of the mean difference) between treatment arms will be reported. Both adjusted and unadjusted random effect linear regression models will be fitted to the data.

6.3.2.7. Secondary outcome: Strawbridge Questionnaire

For each of the four domains of the Strawbridge Questionnaire we will summarise the data into will be summarised into binary categories (rarely or never/sometimes) and (often/very often).

Both adjusted and unadjusted random effect logistics regression models will be fitted to the data.

6.3.2.7 Other secondary outcomes

Other secondary outcomes (mobility/ADLs) will also be summarised using proportions and analysed using appropriate regression models.

6.4 Sub-group Analyses

These sub-group analyses will be conducted on the ITT. They will involve modelling the primary outcome as the independent variable and interaction of treatment and covariate of interest. Thus the modelling will be based on logistic regression and will be analysed in a similar way to the primary outcome (depending on whether clustering is present or not).

Sub-group effects will be tested through formal interaction tests (Brookes et al 2001). Power for sub-group effects is adequate to detect larger interactions provided variance in the sub-groups is reasonably similar (Brookes et al 2001). In addition to formal testing for treatment moderation using an interaction term we will make available either within the primary paper or elsewhere and without drawing inference, the effect sizes and 95% confidence intervals for the main outcomes for each pre-specified sub-group to ensure these data are available for future meta-analysists.

References:

Shua-Haim J, Koppuzha G, Shua-Haim V, Gross J. A simple score system for clock drawing in patients with Alzheimer's disease. *Am J of Alzheimer's Disease* 1997; 12: 212.

Brookes (2001). Health Technol Assess. 2001;5(33):1-56.
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.

Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

Bruce J, Lall R, Withers EJ, Finnegan S, Underwood M, Hulme C, Sheridan R, Skelton DA, Martin F, Lamb SE; PreFIT Study Group A cluster randomised controlled trial of advice, exercise or multifactorial assessment to prevent falls and fractures in community-dwelling older adults: protocol for the prevention of falls injury trial (PreFIT). BMJ Open. 2016 Jan 18;6 (1)

Copsey B, Hopewell S, Becker C, Cameron ID, Lamb SE Appraising the uptake and use of recommendations for a common outcome data set for clinical trials: a case study in fall injury prevention. Trials. 2016 Mar 10;17(1):131.

Kannus P, Niemi S, Parkkari J, Palvanen M, Sievänen H Alarming rise in fall-induced severe head injuries among elderly people. Injury. 2007 Jan;38(1):81-3. Epub 2006 Nov 2.

Palvanen M, Kannus P, Niemi S, Parkkari J. Hospital-treated minimal-trauma rib fractures in elderly Finns: long-term trends and projections for the future. Osteoporos Int. 2004 Aug;15(8):649-53. Epub 2004 Mar 24.

Amin S, Achenbach SJ, Atkinson EJ, Khosla S, Melton LJ 3rd. Trends in fracture incidence: a population-based study over 20 years. J Bone Miner Res. 2014 Mar;29(3):581-9. doi: 10.1002/jbmr.2072.

Korhonen N, Kannus P, Niemi S, Parkkari J, Sievänen H Rapid increase in fall-induced cervical spine injuries among older Finnish adults between 1970 and 2011. Age Ageing. 2014 Jul;43(4):567-71.

Kannus P, Niemi S, Parkkari J, Sievänen H Rising incidence of fall-induced maxillofacial injuries among older adults. Aging Clin Exp Res. 2016 Dec;28(6):1127-1131. Epub 2016 Jan 14.

Appendix 1. Searching for fracture events.

The algorithm for ascertaining fractures has been presented in Bruce et al [2016].

HES APC database.

ICD-10 Diagnosis codes used to identify fracture events in Acute Patient Care (APC) dataset:

A fracture will be assigned if any one of the following occurs

1) A single code report (any one or more of the listed codes)
   a) S02, , S12, S120, S121, S122, S127, S128, S129, S22, S220, S221, S222, S223, S224, S225, S228, S229, S32, S320, S321, S322, S323, S324, S325, S326, S327, S328, S42, S420, S421, S422, S423, S424, S427, S428, S429, S52, S520, S521, S522, S523, S524, S525, S526, S527, S528, S529, S62, S620, S621, S622, S623, S624, S625, S626, S627, S628, S72, S720, S721, S722, S723, S724, S727, S728, S729, S82, S820, S821, S822, S823, S824, S825, S826, S827, S828, S829, S92 S920, S921, S922, S923, S924, S925, S927, S929, T02, T08, T10, T12, T142, Z094, Z544.

   Each reported code will be counted as one fracture. For all fractures, the data of admission will be used as the proxy for date of fracture.

2) A combined code report in the HES Acute Patient Care dataset (one of each list of codes i.e. 2(a) AND 2(b) has to be presented in the same episode record to define a fracture):
   a) M80, M484, M485, M843
   b) W00, W01, W02, W03, W04, W05, W06, W07, W08, W09, W10, W11, W12, W13, W14, W15, W16, W17, W18, W19, or R296

   Each reported code pairing will be counted as one fracture. For all fractures, the data of admission will be used as the proxy for date of fracture.

Notes

In the event that there are single code reports and additional potential fractures identified by the combined code reports, these event records will be adjudicated by SL/MU/KW to determine the total number of events.

Some codes indicate multiple fractures but do not give the number of fractures (e.g. T02 and other S codes). Where possible we will use additional data sources (including other HES data, GP record or self-report to provide a further breakdown of the fracture types and the total number of fractures).

All fractures from the GP records search and HES inpatient record searches will be assigned an ICD code using the ICD schedule below. Where the adjudication team are using ICD code situations such as Colles fracture which can be coded in a number of different ways, a method will be agreed a priori. A record of all adjudications and subsequent codings will be kept and reviewed to ensure consistency. All adjudication will under taken blind to treatment allocation.

List of ICD-10 codes (HES Inpatient/Acute Patient Care)

Code	ICD 10 2010 definition
S02	Fracture of skull and facial bones
S82	Fracture of lower leg, including ankle
T02	Fractures involving multiple body regions
T08	Fracture of spine, level unspecified
T10	Fracture of upper limb, level unspecified
T12	Fracture of lower limb, level unspecified
S120	Fracture of first cervical vertebra
S121	Fracture of second cervical vertebra
S122	Fracture of third cervical vertebra
S127	Multiple fractures of cervical spine
S128	Fracture of other parts of neck
S129	Fracture of neck, unspecified
S220	Fracture of thoracic vertebra
S221	Multiple fractures of thoracic spine
S222	Fracture of sternum
S223	Fracture of one rib
S224	Multiple fractures of ribs
S225	Flail chest
S228	Fracture of other parts of bony thorax
S229	Fracture of bony thorax, part unspecified
S320	Fracture of lumbar vertebra
S321	Fracture of sacrum
S322	Fracture of coccyx

S323	Fracture of ilium
S324	Fracture of acetabulum
S325	Fracture of pubis
S326	Fracture of ischium
S327	Multiple fractures of lumbar spine and pelvis
S328	Fracture of other parts of pelvis
S420	Fracture of clavicle
S421	Fracture of scapula
S422	Fracture of upper end of humerus
S423	Fracture of shaft of humerus
S424	Fracture of lower end of humerus
S427	Multiple fractures of clavicle, scapula and humerus
S428	Fracture of other parts of shoulder and upper arm
S429	Fracture of shoulder girdle, part unspecified
S520	Fracture of upper end of ulna
S521	Fracture of upper end of radius
S522	Fracture of shaft of ulna
S523	Fracture of shaft of radius
S524	Fracture of shafts of both ulna and radius
S525	Fracture of lower end of radius
S526	Fracture of lower end of ulna
S527	Multiple fractures of forearm
S528	Fracture of other parts of forearm
S620	Fracture of navicular [scaphoid] bone of wrist
S621	Fracture of other and unspecified carpal bone(s)
S622	Fracture of first metacarpal bone
S623	Fracture of other and unspecified metacarpal bone
S624	Multiple fractures of metacarpal bones
S625	Fracture of thumb
S626	Fracture of other and unspecified finger(s)
S627	Multiple fractures of fingers

S628	Fracture of other and unspecified parts of wrist and hand
S720	Fracture of head and neck of femur
S721	Pertrochanteric fracture
S722	Subtrochanteric fracture of femur
S723	Fracture of shaft of femur
S724	Fracture of lower end of femur
S727	Multiple fractures of femur
S728	Other fracture of femur
S729	Unspecified fracture of femur
S920	Fracture of calcaneus
S921	Fracture of talus
S922	Fracture of other and unspecified tarsal bone(s)
S923	Fracture of metatarsal bone(s)
S924	Fracture of great toe
S925	Fracture of lesser toe(s)
S927	Multiple fractures of foot
S929	Unspecified fracture of foot and toe
T142	Fracture of unspecified body region
Z094	Follow-up examination after treatment of fracture
Z544	Convalescence following treatment of fracture
M80	Osteoporosis with current pathological fracture
M484	Fatigue fracture of vertebra
M485	Collapsed vertebra, not elsewhere classified
M843	Stress fracture
W00	Fall due to ice and snow
W01	Fall on same level from slipping, tripping and stumbling
W02	Fall involving ice-skates, skis, roller-skates or skateboards
W03	Other fall on same level due to collision with another person
W04	Fall while being carried or supported by other persons

W05	Fall from non-moving wheelchair, nonmotorized scooter and motorized mobility scooter
W06	Fall from bed
W07	Fall from chair
W08	Fall from other furniture
W09	Fall on and from playground equipment
W10	Fall on and from stairs and steps
W11	Fall on and from ladder
W12	Fall on and from scaffolding
W13	Fall from, out of or through building or structure
W14	Fall from tree
W15	Fall from cliff
W16	Fall, jump or diving into water
W17	Other fall from one level to another
W18	Other slipping, tripping and stumbling and falls
W19	Unspecified fall
R296	Repeated falls

List of HES A&E Codes

In addition we will search for HES A&E codes as follows.

Code	Variable	HES Accident & Emergency
	Diagnosis codes	
05	A&E Diagnosis code: 2 character	Dislocation/fracture/joint injury/amputation
052	A&E Diagnosis code: 3 character	Open fracture
053	A&E Diagnosis code: 3 character	Closed fracture
	Treatment codes	
05	A&E Treatment code: 2 character	Plaster of Paris
33	A&E Treatment code: 2 character	Fracture review
101	A&E Treatment code: 3 character	Manipulation of upper limb fracture
102	A&E Treatment code: 3 character	Manipulation of lower limb fracture

All HES A&E codes will be presented for adjudication. Data from patient self-report forms and/or GP record will be used to confirm whether a fracture has occurred (for codes 05), and

for all other codes, we will review GP records and self-report data to ascertain type of fracture by the adjudication committee.

Search strategy for general practice.
A comprehensive search of the general practice patient records (READ Codes) has been undertaken for each practice to identify individuals with suspected fractures from the GP record. All GP records will presented to the adjudication committee to confirm a fracture and fracture details. All fractures will be given an ICD 10 code by the adjudication committee.

Search strategy applied to General Practice searches – Fractures

SEARCHES OF GP READ CODE CLINICAL TERMS, VERSION 2 (CTV 2)	
i. S code search (Any)	Search at higher level "S…." Read code. Download all returns. Then select relevant codes from full detailed READ code listing.
ii. N code (restricted)	Restrict N code searches to:- - N1y1. - N1y2. - N331.
iii. T code (restricted)	- TC7.. [Fracture, cause unspecified]
iii. Free-text "fracture" **iv. Free-text '#' symbol**	Download all returns Download all returns