The administration of intermittent parathyroid hormone affects functional recovery from pertrochanteric fractured neck of femur: A protocol for a prospective mixed method pilot study with randomisation of treatment allocation and blinded assessment. (FRACTT)

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The administration of intermittent parathyroid hormone affects functional recovery from pertrochanteric fractured neck of femur: A protocol for a prospective mixed method pilot study with randomisation of treatment allocation and blinded assessment. (FRACTT)

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ABSTRACT

Introduction

Pertrochanteric hip fractures occur in an elderly population and cause considerable morbidity and loss of functional ability as the fracture heals. Recently parathyroid hormone (PTH), which is licensed for the treatment of osteoporosis, has been shown to potentially accelerate bone healing in animal and human studies. If its administration could allow a faster functional recovery after pertrochanteric hip fracture, then a patient's hospital stay may be reduced and rehabilitation could be potentially accelerated. PTH can currently only be administered by subcutaneous injection. The acceptability of this intervention is unknown in this elderly population. The aim of this pilot study is to inform the design of a future powered study comparing the functional recovery after pertrochanteric hip fracture in patients undergoing standard care, versus those who undergo administration of subcutaneous injection of PTH.

Methods and analysis

The study is an open label, prospective randomised comparative pilot study with blinded outcomes assessment to establish feasibility of the trial design. Patients will be randomised to receive a six-week course of PTH or usual treatment. Functional outcomes will be assessed at six and twelve weeks. Blinded assessment will be used to minimise the effect of bias of an open label study design. A nested qualitative study will investigate the patient experience of, and expectations following, hip fracture and the patient important aspects of recovery compared to the outcome measures proposed.

Results will be analysed to establish the potential recruitment, compliance and retention rates using 95% confidence intervals, and trial outcomes quoted with standard deviations, and 95% confidence intervals for the effect size.

Ethics & Dissemination

The study has been approved by the South West 2 Research Ethics committee. The findings of this study will be disseminated to the medical community via presentations to orthopaedic, orthogeriatric and osteoporosis societies, and their relevant specialist journals.

Trial Registration

ISRCTN Register reference number: ISRCTN03362357

Eudract Number: 2010-020081-22

Strengths

- Blinded Assessments
- Multicentre Randomised Controlled Trial
- Validated outcome Measures used
- Qualitative interview of patient experience

Limitations

- Open Label study
- Pilot study
- Multiple questions
- Vulnerable elderly population

INTRODUCTION

In the United Kingdom (UK) an estimated 70 000 people are admitted to hospital per year due to a hip fracture. The recovery from hip fractures, both in terms of outcome for the

patient, and timescales, requires extensive resources from the health and social services and has great implications on the quality of life and social support for the individual despite the current treatment options available.[1] Patients in this population rarely recover their pre injury mobility and independence.[2,3]

Parathyroid hormone (PTH) is licensed for the treatment of osteoporosis but there is a growing number of animal studies suggesting it can aid fracture healing.[4,5] What is currently unknown is the effectiveness of this for patients who have sustained hip fractures. A short term medical addition of PTH to the current management of these patients has the potential to improve the rate of functional recovery and as a consequence reduce the risks of longer hospital stays, period of dependence on services and potentially quicken functional recovery.

PTH has been shown to improve bone mineral density (BMD) and reduce risk of re-fracture in osteoporotic humans.[6] Pre clinical studies have shown PTH to have a beneficial effect on callus formation, both quality, in terms of trabecular formation, and acceleration of the remodelling phase.[7,8] The proposed mechanism for these effects is thought to be via increasing osteoblast-induced bone formation and proliferation of mesenchymal cells when mediated by Insulin-like Growth Factor 1 (IGF-1). IGF-1 is thought to be stimulated by the inflammatory mediators following a fracture.[9] Therefore PTH influences the amount of bone laid down, and the rate at which the bone is remodelled, achieving an increased amount of bone tissue, including increases in trabecular thickness.[7] This is thought to lead to accelerated healing of fractures. Despite the evidence from animal studies regarding the benefits in treatment of fractures [10-14] the dosage, duration and cost effectiveness of treatment remain in question.[9] Presently subcutaneous injection remains the only licensed administration route [14] and although there are other potential delivery systems under investigation these are not yet licensed for use.[15]

The number of publications, expert reviews and animal studies discussing the role of intermittent PTH in fracture healing in orthopaedic, gerontology and endocrinology literature demonstrates the high level of interest and belief in this new application of PTH. Currently the impact that this treatment may have on patients and their recovery is unknown. The use of a daily injection therapy in elderly acutely injured patients can be viewed as difficult to implement. This pilot study is necessary to investigate how reasonable it is to expect this population to be able to cope with the injection therapy and whether, due to the number of unknown circumstances within the study design, including the proposed outcome measures, it will function appropriately for a full scale, appropriately powered study which will answer the question of efficacy.

Primary Objectives

Objective 1

To establish the potential recruitment, compliance and retention rates for this intervention and trial design to inform sample size calculation, feasibility and design for the full study.

Objective 2

To trial the outcome measures intended for use in the future full study – to test for time and ease of completion in follow up clinics, tolerance of participants and to explore the validity and appropriateness of the suggested measures from the patients' perspective.

Objective 3

To clarify and define 'standard' medicinal care for osteoporotic fractures received by the comparison group.

Objective 4

To establish the feasibility and acceptability of injection therapy over six weeks in the elderly and acutely injured population.

METHODS

This is an open label, prospective randomised comparative pilot study with blinded outcomes assessment to trial the study design. Patients will be randomised to receive PTH or normal treatment. A nested qualitative study will investigate the patient experience of and expectations following hip fracture and the patient important aspects of recovery compared to the outcomes measures proposed.

Sample

Sample Size

This study is intended to be a pilot study to determine whether the methodology is appropriate for a main study with adequate power. As such a suitable sample size for the pilot study was deemed to be 20 per group. Forty patients will be sufficient to provide estimates of standard deviation alongside published literature and twenty patients sufficient to estimate compliance levels to inform a larger adequately powered study. This should also provide sufficient participants for the nested qualitative study (a purposive sample of up to 30 participants) to reach saturation of responses [16] in semi-structured interviews.

Recruitment

Consecutive patients admitted with a pertrochanteric femoral fracture over the age of 60 years will be identified from the orthopaedic trauma units in 6 UK acute care NHS hospitals. Exclusion criteria included the contraindications for the use of PTH detailed in the product literature and those fractures not treated by fixation (table 1).

Exclusion
a. Fracture not as a result of a low energy injury/fall for example fall from standing height
b. Patients whose fracture is managed conservatively
c. Surgical fixation with THR, hemiarthoplasty or cannulated screws
d. Previous treatment with PTH or other PTH analogues
e. Hypersensitivity to the active substance or to any of the excipients
f. Previous IV bisphosphonate (e.g. Zoledronic acid) in the previous 12 months
g. Strontium therapy for osteoporosis within the previous12 months

h. Current medications for breast and prostate cancer (e.g. tamoxifen, anastrozole, zoladex, prostap) or other hormone therapies such as testosterone, HRT
i. Decreased capacity to understand the risks of participating in the trial
j. Pre-existing metabolic bone disease e.g. Pagets disease & hyperparathyroidism other than primary osteoporosis or glucocorticoid-induced osteoporosis
k. Pre-existing hypercalcaemia or high or low corrected calcium which requires investigation
l. Severe renal failure (EGFR <30) or urolithiasis
m. Current unexplained raised alkaline phosphatase
n. Active cancer diagnosis or skeletal malignancies or bone metastases, or prior external beam or implant radiation therapy to skeleton within the last five years
o. Premenopausal
p. Pregnancy or lactation
q. Sustained use of oral steroids
r. Wheelchair, bed bound or transferring only prior to fracture
s. Other current injuries (including fractures) that will affect ability to mobilise at 6 weeks
t. Physically incapable to carry out treatment protocol or appropriate social circumstances (e.g. needle phobia, other severe disabilities limiting manipulation of injection pen and without appropriate carer willing and able to assist).
u. Patient consents to study >7 days post surgery
v. Current participation in any other clinical trial of medicinal product

Table 1 – Exclusion Criteria

Appropriate patients will be approached regarding the study as per International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. They will be provided with a written patient information sheet and the trial will be discussed, including the concept of randomisation and an explanation of the treatment and follow up included in both arms of the trial (including potential side effects of the intervention and potential participation in the qualitative sub study). The patient will be given a minimum of 24 hours to discuss their participation with whomever they choose. They will also be given contact information for the research team during this time for any further information required. Where possible, potential patients will be given as long as required to consider their participation. However, consent will need to be gained and randomisation performed within 7 days of surgery, permitting initiation of the intervention within 10 days post surgery. Randomisation will be performed using the secure online service provided by Sealed Envelope (www.sealedenvelope.com).

Interventions

Parathyroid hormone Intervention Arm

The intervention arm will administer a sub-cutaneous injection of 20µg recombinant PTH (Teriparatide, Eli Lilly) from a prefilled pen daily for six weeks (42 days). Current research suggests a treatment regime of daily subcutaneous injection, between 21 and 56 days,[13,17,18] which closely matches the requirement for subcutaneous injections of low molecular heparin for thromboprohylaxis advised for this patient group.[19] As a consequence a 6 week period of treatment was decided upon for this study due to matching the current requirements for subcutaneous injections for thromboprohylaxis. Additionally, if six weeks does not give a significant benefit, then the clinical improvement anticipated is unlikely to lead to functional improvement for the patient.

A recent study completed by Eli Lilly [18] looked at the effect of intermittent PTH on distal radial fracture healing. Measuring the time to radiographic healing, the results showed a reduced healing time in the 20µg/day treatment group. The results did not show a significant reduction in time to healing measured by cortical bridging on radiograph for the 40µg/day group compared to the placebo group and no dose response was observed between the 20µg/day and 40µg/day groups (given for 8 weeks). This supports the intention to trial 20µg/day. A greater functional difference should be demonstrable in hip fracture healing compared to the upper limb due to the role in weight bearing, essential in activities of daily living. There may be a greater demonstrable effect in the hip fracture population if the extent of osteoporosis is greater. It is recognised by the study group that there is discussion regarding the potential reduction of effect of PTH if there is Vitamin D deficiency [20] and this will therefore be monitored in all patients.

Prescription of Calcium and Vitamin D will continue as per standard treatment. Prescription of other osteoporosis medications such as bisphosphonates or Strontium will be stopped or delayed until following the six-week PTH treatment time. Teriparatide is licensed for the treatment of severe osteoporosis and the prevention of further fragility fracture therefore

delaying the initiation of bisphosphonate therapy does not present any risk to the patients. A review of osteoporosis medication would be indicated as standard care if a patient has been receiving a bone protection medication and has suffered another fragility fracture. After completion of the six weeks PTH treatment time the patient may begin or continue normal osteoporosis treatment which will be prompted by a letter to the participant's General Practitioner.

The participants randomised to the intervention arm will be assisted with the injection in the immediate post-operative phase. They will receive training to administer the injection individually from the clinical or research team prior to discharge and provided with written supporting information. The option of a carer administering the injection will be discussed as appropriate when the situation occurs.

Participants will be asked to return the injection pens to the research team at the six week follow up. This will enable a calculation of compliance to be performed.

Normal Treatment Arm

The normal treatment arm will continue with standard treatment regimens including continuation of or initiation of osteoporosis investigations/medications as per the National Institute for Health and Clinical Excellence (NICE) guidelines (figure 1).[21]

Participants in the pilot study will continue to be referred for Dual-energy X-ray Absorptiometry (DEXA) scans in line with normal care standards, for example as stipulated above in the NICE guidelines [21] or if further investigation is clinically indicated. Both arms of the study will undergo operative fixation, post operative rehabilitation and discharge planning as provided as standard care.

Data Collection

Details regarding eligibility will be recorded during the screening process. Further information regarding questions and concerns posed by those approached will be retained to inform the recruitment information for the full trial and the content of the patient information for the full trial as part of the primary objective. Numbers of patients fulfilling the inclusion criteria not recruited, and where possible, reasons for this will be recorded and monitored to ensure against selective entry and to inform the recruitment process and estimates for the future full trial. Recruitment estimates in the full trial will be based on the recruitment rate from the pilot study in combination with data records of the total eligible patients in each site.

Baseline data (including pre-fracture social circumstances, concomitant illnesses and medications) will be collected following participant recruitment to allow comparisons between groups. The patients' health records/attendance to hospital (and primary care records if required) will be monitored up to one year for incidence of further fracture and mortality, results of DEXA scan and initiation of osteoporosis treatment.

Outcome Measures

The Short Physical Performance Battery (SPPB)[22], 36 item, Short Form health survey, v1 (SF-36), EuroQol (EQ-5D) and Visual Analogue Scale (VAS) for pain on weight bearing measures, will be performed by a blinded trained assessor during outpatient clinic visits at 6 weeks and 3 months post operation. The assessor will be trained by the trial coordinator to ensure consistency and adherence to the trial protocol. Radiograph and compliance information will also be completed as part of their consultation. Patients participating in the nested qualitative study will be asked to repeat all of these assessments during their interviews at 6 and 12 months. Those not participating in the interviews will receive a telephone call to complete the quality of life questionnaires (SF-36 & EQ-5D) at 6 months (figure 2).

Compliance

Patients deviating from any prescribed intervention (intervention or comparative care group) will be encouraged to discuss this with the research team at the 6 week and 3 month follow-ups. The patients in the intervention group will be asked to return their injection pens to the research team at the six week follow up. The remaining contents of the returned pens will be measured enabling an assessment of compliance.

Monitoring adherence to prescribed medications will continue for both comparison and intervention groups until the 12 week follow up to allow an improved definition of 'normal treatment' for the full study. This will include recording which medications, time of starting medication, timing and results of DEXA scan, and tolerance and compliance with their treatment at each follow up stage.

Participants will be made aware throughout that they may withdraw from the study at any stage. In the occurrence of withdrawal from the study patients will be asked if they would inform the research team why they are withdrawing – this is due to the need to establish acceptability of treatment. This would be included in the patient information sheet, and patients would be made aware from the outset. Patients withdrawing/not complying with the injection therapy will be asked if they would continue to participate in follow up for outcome data collection. Patients withdrawing from attending for follow up, unless explicitly withdrawing consent will continue to be monitored for DEXA scan results, further fragility fractures and mortality for 1 year (via hospital or primary care records).

Any participant withdrawing from the study who is part of the qualitative group would be asked if they wished to continue to participate in the semi-structured interviews. This is necessary to establish a true picture of acceptability and success of outcome measures and study design. Patients will be made aware it is their choice whether to take part at each stage.

Safety Reporting & Monitoring

Participants will be asked to report adverse events (AE) at each follow up. The research team will inform the participant's General Practitioner (GP) of the person's inclusion in the trial on discharge from hospital and encourage timely communication of any adverse events experienced during the study. All AE will be recorded in the study paperwork. The trial co-ordinator will maintain a log of adverse events and inform the Chief Investigator (CI). All AE and adverse reactions (AR) for both groups will be collated in a document to enable comparison. The CI and Trial Co-ordinator will jointly collate reports for submission to the Sponsor, Medicines and Healthcare Regulatory Agency (MHRA) and Research Ethics Committee (REC) as required.

All serious adverse events (SAE) and serious adverse reactions (SAR) will be reported to the Sponsor via the Research & Development office and the regulatory authorities per the North Bristol NHS Trust standard operating procedure as soon as the research team is aware of it (within 24 hours) and a written report will follow within seven days as per ICH-GCP guidelines.

The study will be monitored by the North Bristol NHS Trust Research & Innovation office as the sponsor of the study according to their standard operating procedures.

Blinding

The study will be open label due to the complexities of placebo injections in a frail elderly population (both the invasive nature of the intervention and the need to withhold or account for the normal osteoporosis medications for the placebo group). This is the plan for the full study. Blinded assessment of an objective functional score has been included to minimise the bias effect this design may have.

Data Management

All data collection forms are anonymised. The co-ordinating centre will check for any missing data or anomalies that can be addressed by the recruiting site. All data will be coded and manually entered into a Microsoft Access 2003 database. Data validation will occur in 10% of all data entry to minimise transcription error. In the event that there is a >2% error overall the validation will be extended to 20%.

Analysis

Analysis of the feasibility aspects of the pilot study will focus on proportion of patients who were recruited and compliant using 95% confidence intervals calculated using the binomial method.

Statistical analysis for the trial outcomes will be similar to that for the main study but reporting standard deviations of outcome variables and confidence intervals of effect sizes, not investigating statistical significance. The two groups will be compared by tabulating information available at baseline (prior to randomisation). Comparisons of outcome variables following randomisation will be carried out using an intention to treat methodology and an appropriate methodology will be used where follow up outcome data is not available. In the full study this may mean data imputation using regression techniques, but in the pilot study there will be insufficient data to carry out the regressions robustly and last observation carried forward may be used to prevent omission of patients. Treatment effects between the groups will be calculated and confidence intervals calculated. In the full study, in the unlikely event of large differences between the groups at baseline, regression techniques may be employed to demonstrate the treatment effect before and after controlling for these differences.

Thematic analysis of the qualitative data will be undertaken.[16] Interview transcripts will be coded and themes produced from those codes will be used to recommend domains which describe the process of 'recovery' or 'getting better' from the patients' perspective and priorities.

The interviews will be audio-recorded and fully transcribed to allow coding and analysis in an on-going and iterative manner.[23] Interview transcripts will be anonymised using the participants' trial ID. The researcher will code the transcripts according to themes that emerge from the data with supervision from the university supervisors. Data management will be assisted using NVivo software.

ETHICS & DISSEMINATION

The South West 2 Research Ethics Committee has given approval for this study. We will comply with the Medical Research Council Good Clinical Practice guidelines, and the trial will run under the Standard Operating Procedures of North Bristol NHS Trust. An independent data monitoring committee will meet annually, with an option to increase if specific concerns arise. The findings of this study will be disseminated to the medical community via presentations to both orthopaedic, orthogeriatric and osteoporosis societies, and their relevant specialist journals.

COMPETING INTERESTS

The authors declare that they have no completing interests.

AUTHORS CONTRIBUTIONS

TJC & RF conceived the original study and developed the protocol with RH, SB, RG, KH, KJ, SL & KW. Statistical advice was provided by RG. TJC led the writing of the first draft of the

manuscript, with contributions from RH, SB & RF. All authors contributed to the editing and redrafting.

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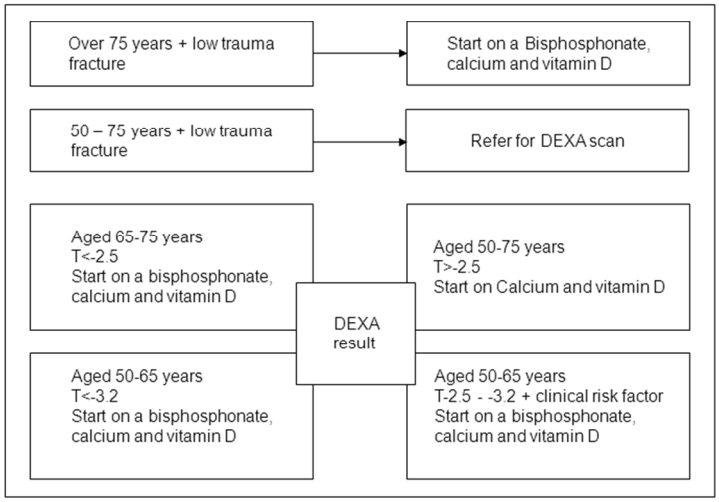
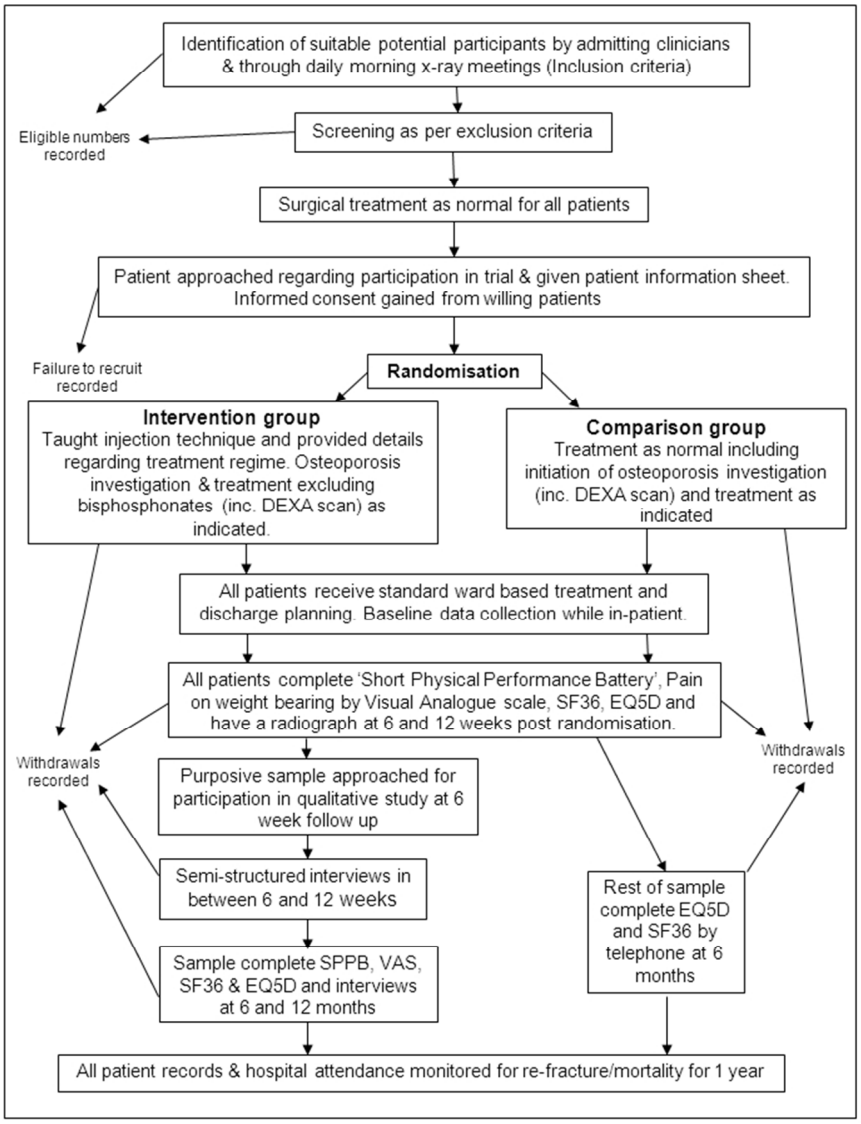
FIGURES

Figure 1 – NICE guidelines for Osteoporosis treatment [21]

Figure 2 – Trial flow diagram





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KEYWORDS

Parathyroid Hormone

Fracture Healing

Recovery of Function

Trochanteric Fractures

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2914 words

ABSTRACT

Introduction

Pertrochanteric hip fractures occur in an elderly population and cause considerable morbidity and loss of functional ability as the fracture heals. Recently parathyroid hormone (PTH), which is licensed for the treatment of osteoporosis, has been shown to potentially accelerate bone healing in animal and human studies. If its administration could allow a faster functional recovery after pertrochanteric hip fracture, then a patient's hospital stay may be reduced and rehabilitation could be potentially accelerated. PTH can currently only be administered by subcutaneous injection. The acceptability of this intervention is unknown in this elderly population. The aim of this pilot study is to inform the design of a future powered study comparing the functional recovery after pertrochanteric hip fracture in patients undergoing standard care, versus those who undergo administration of subcutaneous injection of PTH.

Methods and analysis

The study is an open label, prospective randomised comparative pilot study with blinded outcomes assessment to establish feasibility of the trial design. Patients will be randomised to receive a six-week course of PTH or usual treatment. Functional outcomes will be assessed at six and twelve weeks. Blinded assessment will be used to minimise the effect of bias of an open label study design. A nested qualitative study will investigate the patient experience of, and expectations following, hip fracture and the patient important aspects of recovery compared to the outcome measures proposed.

Results will be analysed to establish the potential recruitment, compliance and retention rates using 95% confidence intervals, and trial outcomes quoted with standard deviations, and 95% confidence intervals for the effect size.

Ethics & Dissemination

The study has been approved by the South West 2 Research Ethics committee (reference 10/H0206/34). The findings of this study will be disseminated to the medical community via presentations to orthopaedic, orthogeriatric and osteoporosis societies, and their relevant specialist journals.

Trial Registration

ISRCTN Register reference number: ISRCTN03362357

Eudract Number: 2010-020081-22

Sponsor

North Bristol NHS Trust – reference NBT R&I 2185

Strengths

- Blinded Assessments
- Multicentre Randomised Controlled Trial
- Validated outcome Measures used
- Qualitative interview of patient experience

Limitations

- Open Label study
- Pilot study
- Multiple questions
- Vulnerable elderly population

INTRODUCTION

In the United Kingdom (UK) an estimated 70 000 people are admitted to hospital per year due to a hip fracture. The recovery from hip fractures, both in terms of outcome for the patient, and timescales, requires extensive resources from the health and social services and has great implications on the quality of life and social support for the individual despite the current treatment options available.[1] Patients in this population rarely recover their pre injury mobility and independence.[2,3]

Parathyroid hormone (PTH) is licensed for the treatment of osteoporosis but there is a growing number of animal studies suggesting it can aid fracture healing.[4,5] What is currently unknown is the effectiveness of this for patients who have sustained hip fractures. A short term medical addition of PTH to the current management of these patients has the potential to improve the rate of functional recovery and as a consequence reduce the risks of longer hospital stays, period of dependence on services and potentially quicken functional recovery.

PTH has been shown to improve bone mineral density (BMD) and reduce risk of re-fracture in osteoporotic humans.[6] Pre clinical studies have shown PTH to have a beneficial effect on callus formation, both quality, in terms of trabecular formation, and acceleration of the remodelling phase.[7,8] The proposed mechanism for these effects is thought to be via increasing osteoblast-induced bone formation and proliferation of mesenchymal cells when mediated by Insulin-like Growth Factor 1 (IGF-1). IGF-1 is thought to be stimulated by the inflammatory mediators following a fracture.[9] Therefore PTH influences the amount of bone laid down, and the rate at which the bone is remodelled, achieving an increased amount of bone tissue, including increases in trabecular thickness.[7] This is thought to lead to accelerated healing of fractures. Despite the evidence from animal studies regarding the benefits in treatment of fractures [10-14] the dosage, duration and cost effectiveness of

treatment remain in question.[9] Presently subcutaneous injection remains the only licensed administration route [14] and although there are other potential delivery systems under investigation these are not yet licensed for use.[15]

The number of publications, expert reviews and animal studies discussing the role of intermittent PTH in fracture healing in orthopaedic, gerontology and endocrinology literature demonstrates the high level of interest and belief in this new application of PTH. Currently the impact that this treatment may have on patients and their recovery is unknown. The use of a daily injection therapy in elderly acutely injured patients can be viewed as difficult to implement. This pilot study is necessary to investigate how reasonable it is to expect this population to be able to cope with the injection therapy and whether, due to the number of unknown circumstances within the study design, including the proposed outcome measures, it will function appropriately for a full scale, appropriately powered study which will answer the question of efficacy.

Primary Objectives

Objective 1

To establish the potential recruitment, compliance and retention rates for this intervention and trial design to inform sample size calculation, feasibility and design for the full study.

Objective 2

To trial the outcome measures intended for use in the future full study – to test for time and ease of completion in follow up clinics, tolerance of participants and to explore the validity and appropriateness of the suggested measures from the patients' perspective.

Objective 3

To clarify and define 'standard' medicinal care for osteoporotic fractures received by the comparison group.

Objective 4

To establish the feasibility and acceptability of injection therapy over six weeks in the elderly and acutely injured population.

METHODS

This is an open label, prospective randomised comparative pilot study with blinded outcomes assessment to trial the study design. Patients will be randomised to receive PTH or normal treatment. A nested qualitative study will investigate the patient experience of and expectations following hip fracture and the patient important aspects of recovery compared to the outcomes measures proposed (figure 1).

Sample

Sample Size

This study is intended to be a pilot study to determine whether the methodology is appropriate for a main study with adequate power. As such a suitable sample size for the pilot study was deemed to be 20 per group. Forty patients will be sufficient to provide estimates of standard deviation alongside published literature and twenty patients sufficient to estimate compliance levels to inform a larger adequately powered study. This should also provide sufficient participants for the nested qualitative study (a purposive sample of up to 30 participants) to reach saturation of responses [16] in semi-structured interviews.

Recruitment

Consecutive patients admitted with a pertrochanteric femoral fracture over the age of 60 years will be identified from the orthopaedic trauma units in 6 UK acute care NHS hospitals. Exclusion criteria included the contraindications for the use of PTH detailed in the product literature and those fractures not treated by fixation (table 1).

Exclusion
a. Fracture not as a result of a low energy injury/fall for example fall from standing height
b. Patients whose fracture is managed conservatively
c. Surgical fixation with THR, hemiarthoplasty or cannulated screws
d. Previous treatment with PTH or other PTH analogues
e. Hypersensitivity to the active substance or to any of the excipients
f. Previous IV bisphosphonate (e.g. Zoledronic acid) in the previous 12 months
g. Strontium therapy for osteoporosis within the previous12 months
h. Current medications for breast and prostate cancer (e.g. tamoxifen, anastrozole, zoladex, prostap) or other hormone therapies such as testosterone, HRT
i. Decreased capacity to understand the risks of participating in the trial
j. Pre-existing metabolic bone disease e.g. Pagets disease & hyperparathyroidism other than primary osteoporosis or glucocorticoid-induced osteoporosis
k. Pre-existing hypercalcaemia or high or low corrected calcium which requires investigation
l. Severe renal failure (EGFR <30) or urolithiasis
m. Current unexplained raised alkaline phosphatase
n. Active cancer diagnosis or skeletal malignancies or bone metastases, or prior external beam or implant radiation therapy to skeleton within the last five years
o. Premenopausal
p. Pregnancy or lactation
q. Sustained use of oral steroids
r. Wheelchair, bed bound or transferring only prior to fracture
s. Other current injuries (including fractures) that will affect ability to mobilise at 6 weeks
t. Physically incapable to carry out treatment protocol or appropriate social circumstances (e.g. needle phobia, other severe disabilities limiting manipulation of injection pen and without appropriate carer willing and able to assist).
u. Patient consents to study >7 days post surgery
v. Current participation in any other clinical trial of medicinal product

Table 1 – Exclusion Criteria

Appropriate patients will be approached regarding the study as per International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. They will be provided with a written patient information sheet and the trial will be discussed, including the concept of randomisation and an explanation of the treatment and follow up included in both arms of the trial (including potential side effects of the intervention and potential participation in the qualitative sub study). The patient will be given a minimum of 24 hours to discuss their participation with whomever they choose. They will also be given contact information for the research team during this time for any further information required. Where possible, potential patients will be given as long as required to consider their participation. However, consent will need to be gained and randomisation performed within 7 days of surgery, permitting

initiation of the intervention within 10 days post surgery. Randomisation will be performed using the secure online service provided by Sealed Envelope (www.sealedenvelope.com).

Interventions

Parathyroid hormone Intervention Arm

The intervention arm will administer a sub-cutaneous injection of 20µg recombinant PTH (Teriparatide, Eli Lilly) from a prefilled pen daily for six weeks (42 days). Current research suggests a treatment regime of daily subcutaneous injection, between 21 and 56 days,[13,17,18] which closely matches the requirement for subcutaneous injections of low molecular heparin for thromboprohylaxis advised for this patient group.[19] As a consequence a 6 week period of treatment was decided upon for this study due to matching the current requirements for subcutaneous injections for thromboprohylaxis. Additionally, if six weeks does not give a significant benefit, then the clinical improvement anticipated is unlikely to lead to functional improvement for the patient.

A recent study completed by Eli Lilly [18] looked at the effect of intermittent PTH on distal radial fracture healing. Measuring the time to radiographic healing, the results showed a reduced healing time in the 20µg/day treatment group. The results did not show a significant reduction in time to healing measured by cortical bridging on radiograph for the 40µg/day group compared to the placebo group and no dose response was observed between the 20µg/day and 40µg/day groups (given for 8 weeks). This supports the intention to trial 20µg/day. A greater functional difference should be demonstrable in hip fracture healing compared to the upper limb due to the role in weight bearing, essential in activities of daily living. There may be a greater demonstrable effect in the hip fracture population if the extent of osteoporosis is greater. It is recognised by the study group that there is discussion regarding the potential reduction of effect of PTH if there is Vitamin D deficiency [20] and this will therefore be monitored in all patients.

Prescription of Calcium and Vitamin D will continue as per standard treatment. Prescription of other osteoporosis medications such as bisphosphonates or Strontium will be stopped or delayed until following the six-week PTH treatment time. Teriparatide is licensed for the treatment of severe osteoporosis and the prevention of further fragility fracture therefore delaying the initiation of bisphosphonate therapy does not present any risk to the patients. A review of osteoporosis medication would be indicated as standard care if a patient has been receiving a bone protection medication and has suffered another fragility fracture. After completion of the six weeks PTH treatment time the patient may begin or continue normal osteoporosis treatment which will be prompted by a letter to the participant's General Practitioner.

The participants randomised to the intervention arm will be assisted with the injection in the immediate post-operative phase. They will receive training to administer the injection individually from the clinical or research team prior to discharge and provided with written supporting information. The option of a carer administering the injection will be discussed as appropriate when the situation occurs.

Participants will be asked to return the injection pens to the research team at the six week follow up. This will enable a calculation of compliance to be performed.

Normal Treatment Arm

The normal treatment arm will continue with standard treatment regimens including continuation of or initiation of osteoporosis investigations/medications as per the National Institute for Health and Clinical Excellence (NICE) guidelines (figure 2).[21]

Participants in the pilot study will continue to be referred for Dual-energy X-ray Absorptiometry (DEXA) scans in line with normal care standards, for example as stipulated above in the NICE guidelines [21] or if further investigation is clinically indicated. Both arms

of the study will undergo operative fixation, post operative rehabilitation and discharge planning as provided as standard care.

Data Collection

Details regarding eligibility will be recorded during the screening process. Further information regarding questions and concerns posed by those approached will be retained to inform the recruitment information for the full trial and the content of the patient information for the full trial as part of the primary objective. Numbers of patients fulfilling the inclusion criteria not recruited, and where possible, reasons for this will be recorded and monitored to ensure against selective entry and to inform the recruitment process and estimates for the future full trial. Recruitment estimates in the full trial will be based on the recruitment rate from the pilot study in combination with data records of the total eligible patients in each site.

Baseline data (including pre-fracture social circumstances, concomitant illnesses and medications) will be collected following participant recruitment to allow comparisons between groups. The patients' health records/attendance to hospital (and primary care records if required) will be monitored up to one year for incidence of further fracture and mortality, results of DEXA scan and initiation of osteoporosis treatment.

Outcome Measures

The Short Physical Performance Battery (SPPB)[22], 36 item, Short Form health survey, v1 (SF-36), EuroQol (EQ-5D) and Visual Analogue Scale (VAS) for pain on weight bearing measures, will be performed by a blinded trained assessor during outpatient clinic visits at 6 weeks and 3 months post operation. The assessor will be trained by the trial coordinator to ensure consistency and adherence to the trial protocol. Radiograph and compliance information will also be completed as part of their consultation. Patients participating in the nested qualitative study will be asked to repeat all of these assessments during their interviews at 6 and 12 months. Those not participating in the interviews will receive a

telephone call to complete the quality of life questionnaires (SF-36 & EQ-5D) at 6 months (figure 3).

Compliance

Patients deviating from any prescribed intervention (intervention or comparative care group) will be encouraged to discuss this with the research team at the 6 week and 3 month follow-ups. The patients in the intervention group will be asked to return their injection pens to the research team at the six week follow up. The remaining contents of the returned pens will be measured enabling an assessment of compliance.

Monitoring adherence to prescribed medications will continue for both comparison and intervention groups until the 12 week follow up to allow an improved definition of 'normal treatment' for the full study. This will include recording which medications, time of starting medication, timing and results of DEXA scan, and tolerance and compliance with their treatment at each follow up stage.

Participants will be made aware throughout that they may withdraw from the study at any stage. In the occurrence of withdrawal from the study patients will be asked if they would inform the research team why they are withdrawing – this is due to the need to establish acceptability of treatment. This would be included in the patient information sheet, and patients would be made aware from the outset. Patients withdrawing/not complying with the injection therapy will be asked if they would continue to participate in follow up for outcome data collection. Patients withdrawing from attending for follow up, unless explicitly withdrawing consent will continue to be monitored for DEXA scan results, further fragility fractures and mortality for 1 year (via hospital or primary care records).

Any participant withdrawing from the study who is part of the qualitative group would be asked if they wished to continue to participate in the semi-structured interviews. This is necessary to establish a true picture of acceptability and success of outcome measures and study design. Patients will be made aware it is their choice whether to take part at each stage.

Safety Reporting & Monitoring

Participants will be asked to report adverse events (AE) at each follow up. The research team will inform the participant's General Practitioner (GP) of the person's inclusion in the trial on discharge from hospital and encourage timely communication of any adverse events experienced during the study. All AE will be recorded in the study paperwork. The trial co-ordinator will maintain a log of adverse events and inform the Chief Investigator (CI). All AE and adverse reactions (AR) for both groups will be collated in a document to enable comparison. The CI and Trial Co-ordinator will jointly collate reports for submission to the Sponsor, Medicines and Healthcare Regulatory Agency (MHRA) and Research Ethics Committee (REC) as required.

All serious adverse events (SAE) and serious adverse reactions (SAR) will be reported to the Sponsor via the Research & Development office and the regulatory authorities per the North Bristol NHS Trust standard operating procedure as soon as the research team is aware of it (within 24 hours) and a written report will follow within seven days as per ICH-GCP guidelines.

The study will be monitored by the North Bristol NHS Trust Research & Innovation office as the sponsor of the study according to their standard operating procedures.

Blinding

The study will be open label due to the complexities of placebo injections in a frail elderly population (both the invasive nature of the intervention and the need to withhold or account for the normal osteoporosis medications for the placebo group). This is the plan for the full study. Blinded assessment of an objective functional score has been included to minimise the bias effect this design may have.

Data Management

All data collection forms are anonymised. The co-ordinating centre will check for any missing data or anomalies that can be addressed by the recruiting site. All data will be coded and manually entered into a Microsoft Access 2003 database. Data validation will occur in 10% of all data entry to minimise transcription error. In the event that there is a >2% error overall the validation will be extended to 20%.

Analysis

Analysis of the feasibility aspects of the pilot study will focus on proportion of patients who were recruited and compliant using 95% confidence intervals calculated using the binomial method.

Statistical analysis for the trial outcomes will be similar to that for the main study but reporting standard deviations of outcome variables and confidence intervals of effect sizes, not investigating statistical significance. The two groups will be compared by tabulating information available at baseline (prior to randomisation). Comparisons of outcome variables following randomisation will be carried out using an intention to treat methodology and an appropriate methodology will be used where follow up outcome data is not available. In the full study this may mean data imputation using regression techniques, but in the pilot study there will be insufficient data to carry out the regressions robustly and last observation

carried forward may be used to prevent omission of patients. Treatment effects between the groups will be calculated and confidence intervals calculated. In the full study, in the unlikely event of large differences between the groups at baseline, regression techniques may be employed to demonstrate the treatment effect before and after controlling for these differences.

Thematic analysis of the qualitative data will be undertaken.[16] Interview transcripts will be coded and themes produced from those codes will be used to recommend domains which describe the process of 'recovery' or 'getting better' from the patients' perspective and priorities.

The interviews will be audio-recorded and fully transcribed to allow coding and analysis in an on-going and iterative manner.[23] Interview transcripts will be anonymised using the participants' trial ID. The researcher will code the transcripts according to themes that emerge from the data with supervision from the university supervisors. Data management will be assisted using NVivo software.

ETHICS & DISSEMINATION

The South West 2 Research Ethics Committee has given approval for this study. We will comply with the Medical Research Council Good Clinical Practice guidelines, and the trial will run under the Standard Operating Procedures of North Bristol NHS Trust. An independent data monitoring committee will meet annually, with an option to increase if specific concerns arise. The findings of this study will be disseminated to the medical community via presentations to both orthopaedic, orthogeriatric and osteoporosis societies, and their relevant specialist journals.

PROTOCOL AMENDMENTS

2010-March-30	Original protocol (approved as a single site study)
2011-Jan-18	Amendment 01: At request of MHRA for authorisation Incorporated changes to wording of exclusion criteria to align these more closely with contraindications to PTH as listed in the SmPC and addition of participant timeline
2011-April-04	Amendment 02: Non-substantial changes to data collection forms
2011-Aug-30	Amendment 03: Protocol amended to incorporate an additional four recruiting sites due to lower potential participant numbers than anticipated
2011-Dec-14	Amendment 04: Change to Oxford PI and addition of three further sites
2012-Feb-01	Amendment 05: Non-substantial amendment. Minor changes to Participant Info Sheet
2012-March-02	Amendment 07: Non-substantial amendment. Minor changes to qualitative Participant Info Sheet
2012-April-16	Amendment 08: Extension to study timescales and revision of target recruitment rate. Addition of recruiting site and removal of recruiting site.
2012-June-25	Amendment 09: Change to Bath PI

Table 2: Protocol amendments

COMPETING INTERESTS

The authors declare that they have no completing interests.

AUTHORS CONTRIBUTIONS

TJC & RF conceived the original study and developed the protocol with RH, SB, RG, KH, KJ, SL & KW. Statistical advice was provided by RG. TJC led the writing of the first draft of the manuscript, with contributions from RH, SB & RF. All authors contributed to the editing and redrafting.

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Trauma Orthopaedic Research Collaboration (TORC) Members

Chair

Professor Keith Willett FRCS, Professor Orthopaedic Surgery

Kadoorie Research Centre, John Radcliffe Hospital, Oxford

Members :

Professor Sallie Lamb, Professor of Rehabilitation,

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Professor Ian Pallister, Consultant Orthopaedic Surgeon, Morriston Hospital,

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FIGURES

Figure 1 – Trial flow diagram

Figure 2 – NICE guidelines for Osteoporosis treatment [21]

Figure 3 – Participant timeline

The administration of intermittent parathyroid hormone affects functional recovery from pertrochanteric fractured neck of femur: A protocol for a prospective mixed method pilot study with randomisation of treatment allocation and blinded assessment. (FRACTT)

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In the United Kingdom (UK) an estimated 70 000 people are admitted to hospital per year due to a hip fracture. The recovery from hip fractures, both in terms of outcome for the patient, and timescales, requires extensive resources from the health and social services and has great implications on the quality of life and social support for the individual despite the current treatment options available.[1] Patients in this population rarely recover their pre injury mobility and independence.[2,3]

Parathyroid hormone (PTH) is licensed for the treatment of osteoporosis but there is a growing number of animal studies suggesting it can aid fracture healing.[4,5] What is currently unknown is the effectiveness of this for patients who have sustained hip fractures. A short term medical addition of PTH to the current management of these patients has the potential to improve the rate of functional recovery and as a consequence reduce the risks of longer hospital stays, period of dependence on services and potentially quicken functional recovery.

PTH has been shown to improve bone mineral density (BMD) and reduce risk of re-fracture in osteoporotic humans.[6] Pre clinical studies have shown PTH to have a beneficial effect on callus formation, both quality, in terms of trabecular formation, and acceleration of the remodelling phase.[7,8] The proposed mechanism for these effects is thought to be via increasing osteoblast-induced bone formation and proliferation of mesenchymal cells when mediated by Insulin-like Growth Factor 1 (IGF-1). IGF-1 is thought to be stimulated by the inflammatory mediators following a fracture.[9] Therefore PTH influences the amount of bone laid down, and the rate at which the bone is remodelled, achieving an increased amount of bone tissue, including increases in trabecular thickness.[7] This is thought to lead to accelerated healing of fractures. Despite the evidence from animal studies regarding the benefits in treatment of fractures [10-14] the dosage, duration and cost effectiveness of

treatment remain in question.[9] Presently subcutaneous injection remains the only licensed administration route [14] and although there are other potential delivery systems under investigation these are not yet licensed for use.[15]

The number of publications, expert reviews and animal studies discussing the role of intermittent PTH in fracture healing in orthopaedic, gerontology and endocrinology literature demonstrates the high level of interest and belief in this new application of PTH. Currently the impact that this treatment may have on patients and their recovery is unknown. The use of a daily injection therapy in elderly acutely injured patients can be viewed as difficult to implement. This pilot study is necessary to investigate how reasonable it is to expect this population to be able to cope with the injection therapy and whether, due to the number of unknown circumstances within the study design, including the proposed outcome measures, it will function appropriately for a full scale, appropriately powered study which will answer the question of efficacy.

Primary Objectives

Objective 1

To establish the potential recruitment, compliance and retention rates for this intervention and trial design to inform sample size calculation, feasibility and design for the full study.

Objective 2

To trial the outcome measures intended for use in the future full study – to test for time and ease of completion in follow up clinics, tolerance of participants and to explore the validity and appropriateness of the suggested measures from the patients' perspective.

Objective 3

To clarify and define 'standard' medicinal care for osteoporotic fractures received by the comparison group.

Objective 4

To establish the feasibility and acceptability of injection therapy over six weeks in the elderly and acutely injured population.

METHODS

This is an open label, prospective randomised comparative pilot study with blinded outcomes assessment to trial the study design. Patients will be randomised to receive PTH or normal treatment. A nested qualitative study will investigate the patient experience of and expectations following hip fracture and the patient important aspects of recovery compared to the outcomes measures proposed (figure 1).

Sample

Sample Size

This study is intended to be a pilot study to determine whether the methodology is appropriate for a main study with adequate power. As such a suitable sample size for the pilot study was deemed to be 20 per group. Forty patients will be sufficient to provide estimates of standard deviation alongside published literature and twenty patients sufficient to estimate compliance levels to inform a larger adequately powered study. This should also provide sufficient participants for the nested qualitative study (a purposive sample of up to 30 participants) to reach saturation of responses [16] in semi-structured interviews.

Recruitment

Consecutive patients admitted with a pertrochanteric femoral fracture over the age of 60 years will be identified from the orthopaedic trauma units in 6 UK acute care NHS hospitals. Exclusion criteria included the contraindications for the use of PTH detailed in the product literature and those fractures not treated by fixation (table 1).

Exclusion
a. Fracture not as a result of a low energy injury/fall for example fall from standing height
b. Patients whose fracture is managed conservatively
c. Surgical fixation with THR, hemiarthoplasty or cannulated screws
d. Previous treatment with PTH or other PTH analogues
e. Hypersensitivity to the active substance or to any of the excipients
f. Previous IV bisphosphonate (e.g. Zoledronic acid) in the previous 12 months
g. Strontium therapy for osteoporosis within the previous12 months
h. Current medications for breast and prostate cancer (e.g. tamoxifen, anastrozole, zoladex, prostap) or other hormone therapies such as testosterone, HRT
i. Decreased capacity to understand the risks of participating in the trial
j. Pre-existing metabolic bone disease e.g. Pagets disease & hyperparathyroidism other than primary osteoporosis or glucocorticoid-induced osteoporosis
k. Pre-existing hypercalcaemia or high or low corrected calcium which requires investigation
l. Severe renal failure (EGFR <30) or urolithiasis
m. Current unexplained raised alkaline phosphatase
n. Active cancer diagnosis or skeletal malignancies or bone metastases, or prior external beam or implant radiation therapy to skeleton within the last five years
o. Premenopausal
p. Pregnancy or lactation
q. Sustained use of oral steroids
r. Wheelchair, bed bound or transferring only prior to fracture
s. Other current injuries (including fractures) that will affect ability to mobilise at 6 weeks
t. Physically incapable to carry out treatment protocol or appropriate social circumstances (e.g. needle phobia, other severe disabilities limiting manipulation of injection pen and without appropriate carer willing and able to assist).
u. Patient consents to study >7 days post surgery
v. Current participation in any other clinical trial of medicinal product

Table 1 – Exclusion Criteria

Appropriate patients will be approached regarding the study as per International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. They will be provided with a written patient information sheet and the trial will be discussed, including the concept of randomisation and an explanation of the treatment and follow up included in both arms of the trial (including potential side effects of the intervention and potential participation in the qualitative sub study). The patient will be given a minimum of 24 hours to discuss their participation with whomever they choose. They will also be given contact information for the research team during this time for any further information required. Where possible, potential patients will be given as long as required to consider their participation. However, consent will need to be gained and randomisation performed within 7 days of surgery, permitting

initiation of the intervention within 10 days post surgery. Randomisation will be performed using the secure online service provided by Sealed Envelope (www.sealedenvelope.com).

Interventions

Parathyroid hormone Intervention Arm

The intervention arm will administer a sub-cutaneous injection of 20µg recombinant PTH (Teriparatide, Eli Lilly) from a prefilled pen daily for six weeks (42 days). Current research suggests a treatment regime of daily subcutaneous injection, between 21 and 56 days,[13,17,18] which closely matches the requirement for subcutaneous injections of low molecular heparin for thromboprohylaxis advised for this patient group.[19] As a consequence a 6 week period of treatment was decided upon for this study due to matching the current requirements for subcutaneous injections for thromboprohylaxis. Additionally, if six weeks does not give a significant benefit, then the clinical improvement anticipated is unlikely to lead to functional improvement for the patient.

A recent study completed by Eli Lilly [18] looked at the effect of intermittent PTH on distal radial fracture healing. Measuring the time to radiographic healing, the results showed a reduced healing time in the 20µg/day treatment group. The results did not show a significant reduction in time to healing measured by cortical bridging on radiograph for the 40µg/day group compared to the placebo group and no dose response was observed between the 20µg/day and 40µg/day groups (given for 8 weeks). This supports the intention to trial 20µg/day. A greater functional difference should be demonstrable in hip fracture healing compared to the upper limb due to the role in weight bearing, essential in activities of daily living. There may be a greater demonstrable effect in the hip fracture population if the extent of osteoporosis is greater. It is recognised by the study group that there is discussion regarding the potential reduction of effect of PTH if there is Vitamin D deficiency [20] and this will therefore be monitored in all patients.

Prescription of Calcium and Vitamin D will continue as per standard treatment. Prescription of other osteoporosis medications such as bisphosphonates or Strontium will be stopped or delayed until following the six-week PTH treatment time. Teriparatide is licensed for the treatment of severe osteoporosis and the prevention of further fragility fracture therefore delaying the initiation of bisphosphonate therapy does not present any risk to the patients. A review of osteoporosis medication would be indicated as standard care if a patient has been receiving a bone protection medication and has suffered another fragility fracture. After completion of the six weeks PTH treatment time the patient may begin or continue normal osteoporosis treatment which will be prompted by a letter to the participant's General Practitioner.

The participants randomised to the intervention arm will be assisted with the injection in the immediate post-operative phase. They will receive training to administer the injection individually from the clinical or research team prior to discharge and provided with written supporting information. The option of a carer administering the injection will be discussed as appropriate when the situation occurs.

Participants will be asked to return the injection pens to the research team at the six week follow up. This will enable a calculation of compliance to be performed.

Normal Treatment Arm

The normal treatment arm will continue with standard treatment regimens including continuation of or initiation of osteoporosis investigations/medications as per the National Institute for Health and Clinical Excellence (NICE) guidelines (figure 2~~1~~).[21]

Participants in the pilot study will continue to be referred for Dual-energy X-ray Absorptiometry (DEXA) scans in line with normal care standards, for example as stipulated above in the NICE guidelines [21] or if further investigation is clinically indicated. Both arms

of the study will undergo operative fixation, post operative rehabilitation and discharge planning as provided as standard care.

Data Collection

Details regarding eligibility will be recorded during the screening process. Further information regarding questions and concerns posed by those approached will be retained to inform the recruitment information for the full trial and the content of the patient information for the full trial as part of the primary objective. Numbers of patients fulfilling the inclusion criteria not recruited, and where possible, reasons for this will be recorded and monitored to ensure against selective entry and to inform the recruitment process and estimates for the future full trial. Recruitment estimates in the full trial will be based on the recruitment rate from the pilot study in combination with data records of the total eligible patients in each site.

Baseline data (including pre-fracture social circumstances, concomitant illnesses and medications) will be collected following participant recruitment to allow comparisons between groups. The patients' health records/attendance to hospital (and primary care records if required) will be monitored up to one year for incidence of further fracture and mortality, results of DEXA scan and initiation of osteoporosis treatment.

Outcome Measures

The Short Physical Performance Battery (SPPB)[22], 36 item, Short Form health survey, v1 (SF-36), EuroQol (EQ-5D) and Visual Analogue Scale (VAS) for pain on weight bearing measures, will be performed by a blinded trained assessor during outpatient clinic visits at 6 weeks and 3 months post operation. The assessor will be trained by the trial coordinator to ensure consistency and adherence to the trial protocol. Radiograph and compliance information will also be completed as part of their consultation. Patients participating in the nested qualitative study will be asked to repeat all of these assessments during their interviews at 6 and 12 months. Those not participating in the interviews will receive a

telephone call to complete the quality of life questionnaires (SF-36 & EQ-5D) at 6 months (figure 3~~2~~).

Compliance

Patients deviating from any prescribed intervention (intervention or comparative care group) will be encouraged to discuss this with the research team at the 6 week and 3 month follow-ups. The patients in the intervention group will be asked to return their injection pens to the research team at the six week follow up. The remaining contents of the returned pens will be measured enabling an assessment of compliance.

Monitoring adherence to prescribed medications will continue for both comparison and intervention groups until the 12 week follow up to allow an improved definition of 'normal treatment' for the full study. This will include recording which medications, time of starting medication, timing and results of DEXA scan, and tolerance and compliance with their treatment at each follow up stage.

Participants will be made aware throughout that they may withdraw from the study at any stage. In the occurrence of withdrawal from the study patients will be asked if they would inform the research team why they are withdrawing – this is due to the need to establish acceptability of treatment. This would be included in the patient information sheet, and patients would be made aware from the outset. Patients withdrawing/not complying with the injection therapy will be asked if they would continue to participate in follow up for outcome data collection. Patients withdrawing from attending for follow up, unless explicitly withdrawing consent will continue to be monitored for DEXA scan results, further fragility fractures and mortality for 1 year (via hospital or primary care records).

Any participant withdrawing from the study who is part of the qualitative group would be asked if they wished to continue to participate in the semi-structured interviews. This is necessary to establish a true picture of acceptability and success of outcome measures and study design. Patients will be made aware it is their choice whether to take part at each stage.

Safety Reporting & Monitoring

Participants will be asked to report adverse events (AE) at each follow up. The research team will inform the participant's General Practitioner (GP) of the person's inclusion in the trial on discharge from hospital and encourage timely communication of any adverse events experienced during the study. All AE will be recorded in the study paperwork. The trial co-ordinator will maintain a log of adverse events and inform the Chief Investigator (CI). All AE and adverse reactions (AR) for both groups will be collated in a document to enable comparison. The CI and Trial Co-ordinator will jointly collate reports for submission to the Sponsor, Medicines and Healthcare Regulatory Agency (MHRA) and Research Ethics Committee (REC) as required.

All serious adverse events (SAE) and serious adverse reactions (SAR) will be reported to the Sponsor via the Research & Development office and the regulatory authorities per the North Bristol NHS Trust standard operating procedure as soon as the research team is aware of it (within 24 hours) and a written report will follow within seven days as per ICH-GCP guidelines.

The study will be monitored by the North Bristol NHS Trust Research & Innovation office as the sponsor of the study according to their standard operating procedures.

Blinding

The study will be open label due to the complexities of placebo injections in a frail elderly population (both the invasive nature of the intervention and the need to withhold or account for the normal osteoporosis medications for the placebo group). This is the plan for the full study. Blinded assessment of an objective functional score has been included to minimise the bias effect this design may have.

Data Management

All data collection forms are anonymised. The co-ordinating centre will check for any missing data or anomalies that can be addressed by the recruiting site. All data will be coded and manually entered into a Microsoft Access 2003 database. Data validation will occur in 10% of all data entry to minimise transcription error. In the event that there is a >2% error overall the validation will be extended to 20%.

Analysis

Analysis of the feasibility aspects of the pilot study will focus on proportion of patients who were recruited and compliant using 95% confidence intervals calculated using the binomial method.

Statistical analysis for the trial outcomes will be similar to that for the main study but reporting standard deviations of outcome variables and confidence intervals of effect sizes, not investigating statistical significance. The two groups will be compared by tabulating information available at baseline (prior to randomisation). Comparisons of outcome variables following randomisation will be carried out using an intention to treat methodology and an appropriate methodology will be used where follow up outcome data is not available. In the full study this may mean data imputation using regression techniques, but in the pilot study there will be insufficient data to carry out the regressions robustly and last observation

carried forward may be used to prevent omission of patients. Treatment effects between the groups will be calculated and confidence intervals calculated. In the full study, in the unlikely event of large differences between the groups at baseline, regression techniques may be employed to demonstrate the treatment effect before and after controlling for these differences.

Thematic analysis of the qualitative data will be undertaken.[16] Interview transcripts will be coded and themes produced from those codes will be used to recommend domains which describe the process of 'recovery' or 'getting better' from the patients' perspective and priorities.

The interviews will be audio-recorded and fully transcribed to allow coding and analysis in an on-going and iterative manner.[23] Interview transcripts will be anonymised using the participants' trial ID. The researcher will code the transcripts according to themes that emerge from the data with supervision from the university supervisors. Data management will be assisted using NVivo software.

ETHICS & DISSEMINATION

The South West 2 Research Ethics Committee has given approval for this study. We will comply with the Medical Research Council Good Clinical Practice guidelines, and the trial will run under the Standard Operating Procedures of North Bristol NHS Trust. An independent data monitoring committee will meet annually, with an option to increase if specific concerns arise. The findings of this study will be disseminated to the medical community via presentations to both orthopaedic, orthogeriatric and osteoporosis societies, and their relevant specialist journals.

PROTOCOL AMENDMENTS

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2010-March-30	Original protocol (approved as a single site study)
2011-Jan-18	Amendment 01: At request of MHRA for authorisation Incorporated changes to wording of exclusion criteria to align these more closely with contraindications to PTH as listed in the SmPC and addition of participant timeline
2011-April-04	Amendment 02: Non-substantial changes to data collection forms
2011-Aug-30	Amendment 03: Protocol amended to incorporate an additional four recruiting sites due to lower potential participant numbers than anticipated
2011-Dec-14	Amendment 04: Change to Oxford PI and addition of three further sites
2012-Feb-01	Amendment 05: Non-substantial amendment. Minor changes to Participant Info Sheet
2012-March-02	Amendment 07: Non-substantial amendment. Minor changes to qualitative Participant Info Sheet
2012-April-16	Amendment 08: Extension to study timescales and revision of target recruitment rate. Addition of recruiting site and removal of recruiting site.
2012-June-25	Amendment 09: Change to Bath PI

Table 2: Protocol amendments

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COMPETING INTERESTS

The authors declare that they have no completing interests.

AUTHORS CONTRIBUTIONS

TJC & RF conceived the original study and developed the protocol with RH, SB, RG, KH, KJ, SL & KW. Statistical advice was provided by RG. TJC led the writing of the first draft of the manuscript, with contributions from RH, SB & RF. All authors contributed to the editing and redrafting.

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Chair

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Kadoorie Research Centre, John Radcliffe Hospital, Oxford

Members :

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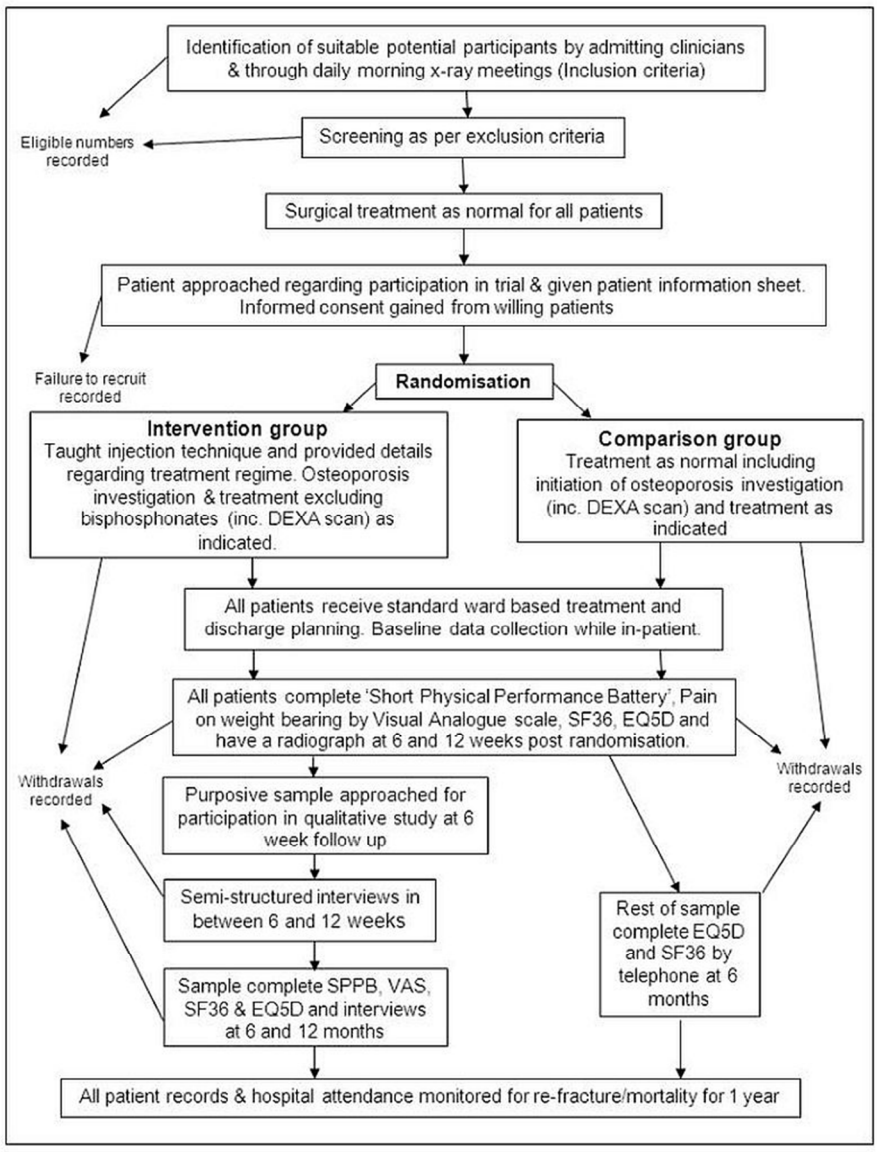
FIGURES

Figure 1 – Trial flow diagram ~~NICE guidelines for Osteoporosis treatment [21]~~

Figure 2 – NICE guidelines for Osteoporosis treatment [21]

Figure 3 – Participant timeline~~Trial flow diagram~~



Trial flow diagram
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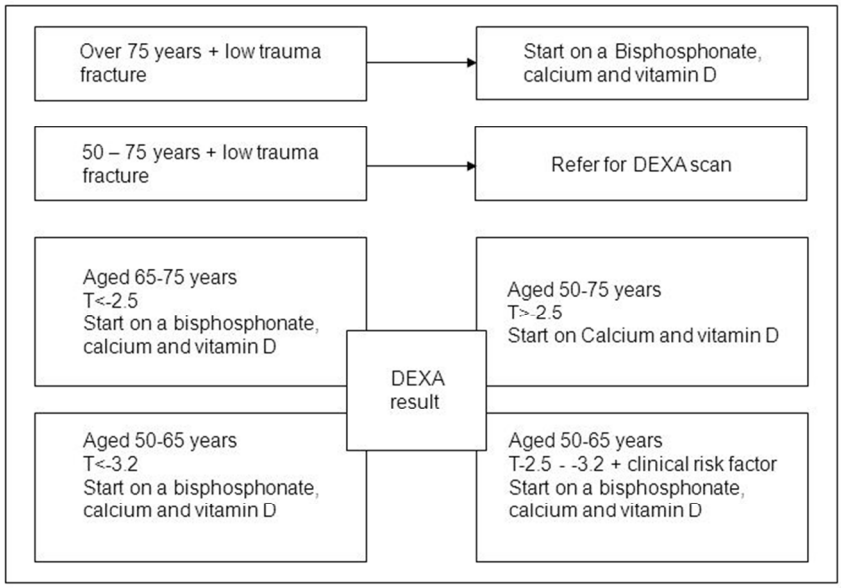

NICE guidelines
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	Screening	Randomisation ≤ 7 days post #	End of In-pt stay	6 weeks	12 weeks	6 months	12 months
Informed consent	x						
Review Inclusion and exclusion criteria	x						
Participant ID assigned	x						
Randomisation		x					
Baseline data set		x	x				
Radiological assessment # fixation				x	x		
Compliance measurement				x			
Collection of osteoporosis investigation treatment data			x	x	x		
SPPB				x	x	Qual group	Qual group
VAS pain				x	x	Qual group	Qual group
SF-36				x	x	x	Qual group
EQ5D				x	x	x	Qual group
Qualitative interview					Qual group	Qual group	Qual group
Monitoring for further fragility fracture			x	x	x	x	x
Lost to follow up or withdrawal of consent recorded			x	x	x	x	x
Adverse event recording			x	x	x	x	x
Mortality		x	x	x	x	x	x

Participant timeline
262x90mm (300 x 300 DPI)