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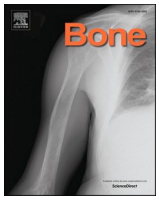

Utility of PINP to monitor osteoporosis treatment in primary care, the POSE study (PINP and Osteoporosis in Sheffield Evaluation)

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ABSTRACT

Purpose: In Sheffield (UK), we introduced the PINP monitoring algorithm for the management of osteoporosis treatment delivered in primary care. Our aims were to evaluate whether this algorithm was associated with better osteoporosis outcomes and was cost-effective compared to standard care.

Methods: Inclusion criteria were referral from Sheffield GPs, BMD scans performed between 2012 and 2013 and a report advising initiation of oral bisphosphonate and PINP monitoring. 906 patients were identified and retrospectively divided into Group A (intention to monitor, with baseline PINP, $n = 588$) and Group B (no intention to monitor, without baseline PINP, $n = 318$). The model described by Davis and colleagues was used to extrapolate life-time costs and quality-adjusted life-years (QALYs).

Results: No differences were found in baseline characteristics between groups (age, gender, BMI, BMD and major risk factors for fractures). More patients in Group A started oral treatment (77.4% vs 49.1%; $p < 0.001$), but there were no differences between groups in the presence of a gap in treatment >3 months or in treatment duration. Patients in Group A were more likely to have follow-up DXA scan at 4–6 years from baseline (46.9% vs 29.2%; $p < 0.000$) and had a greater increase in total hip BMD (+2.74% vs + 0.42%; p value = 0.003). Fewer new fractures occurred in Group A but this was not statistically significant, but the numbers of fractures were small. Patients in Group A were more likely to change management ($p = 0.005$) including switching to zoledronate ($p = 0.03$). The PINP measurement and increased prescribing in Group A resulted in increases in both costs (£30.19) and QALYs (0.0039) relative to Group B, giving an incremental cost effectiveness ratio (ICER) of £7660 in the probabilistic sensitivity analysis.

Conclusions: Patients monitored with PINP are more likely to start oral bisphosphonate treatment, switch to zoledronate, have follow-up DXA scans and a greater increase of hip BMD. PINP monitoring has the potential to be cost-effective in a UK NHS setting given that interventions with an ICER under £20,000 are generally considered to be cost-effective.

1. Introduction

Oral bisphosphonates are the usual first-line therapy for osteoporosis and serial bone mineral density (BMD) measurements by dual-energy X-ray absorptiometry (DXA) at the spine and hip every 1 to 3 years are suggested to monitor and assess the response to treatment [1]. However, even though BMD is a very strong predictor of osteoporotic fractures, it has some limitations in the diagnostic assessment because it does not take into account strength and qualitative properties of the bone and fragility fractures commonly occur in people with BMD above the World Health Organisation osteoporosis threshold [2]. Furthermore, the use of BMD measurement to monitor treatment response is limited as changes in BMD occur over many months or years and an earlier and cheaper evaluation of adherence and identification of poor response to treatment would be useful [3]. Biomarkers of collagen synthesis and degradation have been validated against the gold standard bone histomorphometry

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from transiliac biopsies [4] and become widely used to assess bone turnover because of their low cost and easily accessible assays [3]. The International Osteoporosis Foundation (IOF) and European Calcified Tissue Society (ECTS) Working Group recommended the use of bone turnover markers (BTMs) to assess the adherence to oral bisphosphonates and they proposed C-terminal telopeptide of type I collagen (CTX) and N-propeptide of type I collagen (PINP) as the reference markers for bone resorption and bone formation, respectively [5]. They suggested measurement of PINP or CTX before starting oral bisphosphonates, then reassessment of the bone markers levels after 3 months to verify if the decrease exceeds the least significant change (LSC).

At the Metabolic Bone Centre (MBC) at the Sheffield Teaching Hospitals NHS Foundation Trust, patients are referred for BMD measurements mainly via their general practitioner (GP), if they have risk factors for osteoporosis or if they have had fractures. The scan is reported by one of the doctors working at the MBC and in some occasions, treatment is recommended. In the past, GPs were advised to repeat DXA scan after 2 years of treatment. We introduced PINP as a bone turnover marker for monitoring osteoporosis treatment in 2011 and developed a monitoring algorithm (Fig. 1) for anti-resorptive treatment in primary care [3]. Following our protocol, GPs are advised to perform a baseline PINP before starting treatment, check compliance at 1 month and perform a follow-up PINP at 6 months. The recommendations are made using standard autotext in the DXA report which includes a hyperlink to the PINP monitoring protocol, in addition to recommendation for treatment. Based on the results of the TRIO study [6], a good response is considered a reduction of more than 10 μg/l (LSC) or a decrease below 35 μg/l, which is the average value for premenopausal women [3]. Providing PINP demonstrates a good response at 6 months, the algorithm recommends that oral bisphosphonates should be continued up to 5 years, at which time the clinician should reassess fracture risk and BMD using DXA and consider the pros and cons of a "drug holiday". However, in case of suboptimal PINP response, further evaluations are needed in order to investigate the failure of treatment.

Thanks to this long experience in the use of BTMs to monitor anti-osteoporosis treatment, we have a large cohort of patients treated for osteoporosis by GPs with PINP monitoring and for whom 5-year follow-up is available. This provided us the opportunity to evaluate, in a real-world setting, whether PINP monitoring improves outcome of osteoporosis treatment delivered in primary care. The POSE study (PINP and Osteoporosis in Sheffield Evaluation) aims to evaluate the clinical utility of the Sheffield pathway to monitor osteoporosis treatment in primary care. The aims of the study were to evaluate whether PINP monitoring was associated with better treatment acceptance and persistence, higher likelihood of BMD increases and reduced risk of incident fractures and more likely change of management; moreover, we aimed to evaluate the cost-effectiveness of PINP monitoring compared to standard care without PINP monitoring.

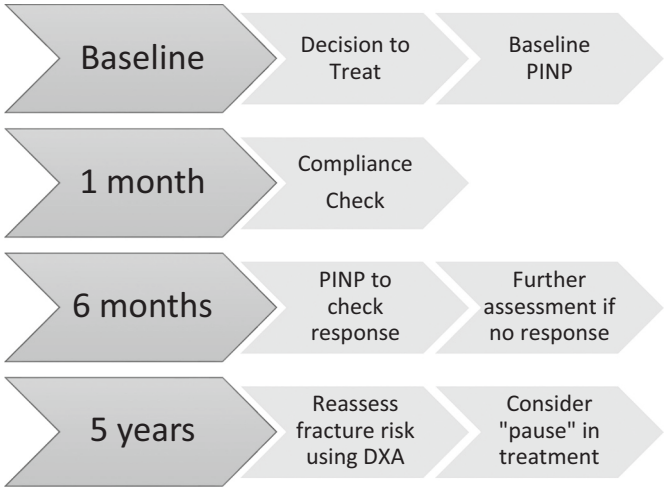

Fig. 1. Sheffield PINP monitoring algorithm for anti-resorptive treatment (modified from [3]).

2. Materials and methods

2.1. Patient information

This observational cohort study was a retrospective analysis of clinical data from the Metabolic Bone Centre (MBC) of Sheffield Teaching Hospitals NHS Foundation Trust. Data collection has been carried out using information from the departmental database and using systems available on NHS computers: fracture risk assessment reports, Picture Archiving and Communications System (PACS) and CRIS (imaging and workflow systems), ICE (laboratory and imaging reports), Lorenzo (electronic record for secondary care), Clinical portal (enables limited access to primary care clinical information).

We identified a cohort of 906 patients who met the following inclusion criteria: 1. fracture risk assessment including DXA scans performed in our department between 01/01/2012 and 31/12/2013; 2. patients referred from primary care in Sheffield. All PINP measurements from Sheffield GPs were performed in Sheffield Teaching Hospitals clinical laboratory, using the same method (Elecsys® total PINP assay run on a Cobas® autoanalyzer - Roche Diagnostics GmbH, Mannheim, Germany) and were identified using ICE.

We collected data on patients' characteristics (date of birth, gender, postcode, weight and height at baseline) and baseline DXA scan (Hologic, Marlborough, Massachusetts, United States): scan date, reason for referral, referrer ID-, scan results (lumbar spine, total hip and femoral neck T-score, *Z*-score and BMD), vertebral fracture assessment (VFA) results. The T-scores for hip BMD are calculated using the NHANEs database, while the manufacturer's database is used for the calculation of the lumbar spine T-scores and Z-scores.

From the baseline DXA reports, we collected the results of any investigations for secondary osteoporosis (performed in case of *Z*-score $\leq$ 2, vertebral fractures or unexpected bone loss) and assessed the presence of any risk factors for osteoporosis, such as history of previous fractures, smoking and excessive alcohol intake. We also checked vitamin D supplementation and calculated FRAX score for major osteoporosis and hip fractures. Where accessible, we collected information from the primary care record about treatment initiation, duration, reason for stopping and possible change in management (referral to our department in MBC, change to intravenous zoledronic acid, change to other medication).

We collected follow-up DXA scan results and VFA results if performed in accordance with the algorithm at 4–6 years from baseline, evaluating changes in BMD and incidence of new fractures. Information about new fractures originated from a patient questionnaire, the results of which were included in the follow-up DXA reports. Available X-rays were also reviewed to check for fractures whenever possible. Moreover, we collected PINP values and dates of the assessment.

2.2. Definitions and analysis

The patients have been divided into two groups: the *intention to monitor* group (Group A) includes patients who had a baseline PINP measurement performed up to 3 months before or after the baseline DXA scan; the *no intention to monitor* group (Group B) includes patients without a baseline PINP assessment. In group A, we can identify two subgroups of patients, based on the availability of a follow-up PINP, which we defined as a PINP measurement performed at 4–9 months from the baseline PINP. In this subgroup, we described a good response to treatment (responder patient) as a drop of more than 10 μg/l and/or a drop below 35 μg/l from the baseline PINP. If a compliance issue is identified, the algorithm recommends the patient should be re-educated and re-monitored after an appropriate length of time. In case of multiple

PINP measurements performed within 4–9 months from baseline, we considered the last measurement available to assess response.

We evaluated persistence and treatment duration using the following ways: presence/absence of gap in prescriptions of more than 3 months and duration of treatment prior to the presence of gap. In a further analysis, we evaluated patients that had taken oral bisphosphonates for at least 5 years. We also assessed differences between Group A and Group B in terms of BMD change, the occurrence of new fractures during the follow-up and changes in management (referral to MBC clinics, switch to intravenous bisphosphonate treatment or to other medications). We finally studied the rate of PINP responder patients and tried to evaluate the underlying reason for non-response.

The statistical analysis was performed with the support of IBM SPSS Statistics software Version 26. Independent *t*-test or chi-square test was used to test the difference between groups for numerical and categorical data, respectively, and a p value <0.05 was considered as cut-off for statistical significance.

2.3. Cost effectiveness analysis

A health economic analysis was conducted to assess the impact of PINP monitoring on life-time costs and quality-adjusted life-years (QALYs) compared with standard care without PINP monitoring. The analysis focused on estimating the impact of PINP monitoring on the usage of anti-fracture medication. This is based on the premise that GPs may be more likely to switch patients from oral to i.v. bisphosphonates if there is a lack of treatment response detected at the follow-up PINP. Data from the observational cohort were used to determine the proportion of patients in Group A and Group B following one of four treatment pathways;

a) Treatment with oral bisphosphonates without switching to zoledronate
b) Treatment with i.v. zoledronate without first starting oral bisphosphonates
c) Treatment with oral bisphosphonates followed by treatment with zoledronate
d) Neither oral bisphosphonates nor i.v. zoledronate treatment started.

The allocation of patients to one of these four pathways based on the data available is a simplification which facilitates the long-term extrapolation of costs and benefits by allowing these to be estimated for groups of patients following similar pathways rather than attempting to model the exact treatment received by individuals. We assumed that the usage of antifracture medications other than oral and i.v. bisphosphonates did not differ between Groups A and B. Further details on the assumptions used to allocate patients to one of the four treatment pathways are provided in the Supplementary appendix, including the assumptions applied when there were missing data (Figs. S1 and S2). Information on the average duration of treatment for each element of pathways 1 to 3 was also estimated from the cohort. Details on the proportions following each treatment pathway and the mean duration of treatment applied are also provided in the Supplementary appendix (Tables S1 and S2).

An existing published cost-effectiveness model described by Davis et al. was then used to extrapolate life-time incremental costs and QALYs for pathways 1 to 3 relative to pathway 4 [7]. The model uses a discrete event simulation (DES) framework. The key clinical events modelled are fractures at the hip, vertebrae, wrist or proximal humerus, all-cause mortality and fracture-related mortality; the latter is only possible following hip or vertebral fractures. Fractures are associated with an acute cost in the year of fracture and an ongoing cost in subsequent years. Costs are estimated from an NHS and Personal Social Services perspective including costs incurred in primary and secondary care and social care provided in the home. In addition, hip fractures are also associated with an increased risk of new admission to a residential care home with an associated cost for a proportion of patients whose residential care is not self-funded. Fractures are associated with a reduction in quality-of-life, with separate decrements applied in the first and subsequent years. A further quality-of-life decrement is applied to patients admitted to a nursing home following fracture. The prevention of fractures therefore results in QALY gains through the avoidance of these quality-of-life decrements in addition to the QALY gains achieved by preventing fracture-related mortality.

The model is a patient-level simulation that takes into account the heterogeneous patient characteristics present within the population being simulated. We specified patient characteristics for a cohort of 50,000 patients by repeatedly sampling patient characteristics from the observational cohort. Where data were unavailable for specific risk factors we sampled these based on the general population prevalence of those risk factors according to methods used previously by Davis et al. [7]. The model uses the QFracture algorithm [8] to estimate the risk of fracture when receiving no anti-fracture medication according to each patient's characteristics. The model applies the hazard ratios for fracture estimated from a network meta-analysis also reported by Davis et al. [7] to estimate fracture risks for each treatment pathway.

In accordance with the criteria used in the observational cohort, all patients in the Group A received a first PINP and the proportion receiving a follow-up PINP is based on resource use in the cohort. The cost to GPs of a PINP test is £12.50 based on cost estimates from Sheffield Teaching Hospitals NHS Foundation Trust (STH NHS FT) (personal communication, R Eastell, 21st Jan 2021). The model assumes that patients who are initiated on treatment will be scheduled to receive a DXA scan at the end of treatment (i.e. at 5 years for oral bisphosphonates and 3 years for i.v. zoledronate). A unit cost for DXA of £100 has been applied based on a local estimate from STH NHS FT (personal communication, R Eastell, 21st Jan 2021). This cost covers DXA scan and additional investigations automatically included on the basis of clinical criteria, such as vertebral fracture assessment (VFA), laboratory tests and spine X-rays. We have assumed that PINP monitoring does not increase secondary care referrals.

No administration costs are applied for oral bisphosphonates. On the other hand, GPs in Sheffield can refer patients for i.v. bisphosphonate treatment via a direct-access pathway and this incurs costs for secondary care outpatient attendances. The cost of a day-case administration of a simple parenteral chemotherapy was used by Davis et al. as a proxy for a day-case i.v. infusion of zoledronate as no suitable reference cost could be identified [7]. Rather than using this proxy unit cost, we have applied an average cost of £480 based on the average cost for day-case administration of zoledronate across both complex and non-complex cases provided by STH NHS FT (personal communication, R Eastell, 21st Jan 2021).

Drug costs for oral bisphosphonates are based on the December 2020 NHS Drug Tariff and these assume that the lowest cost preparation of generic alendronate is prescribed [9]. Drug costs for i.v. zoledronate are based on the eMIT database which provides the average costs for generic drugs prescribed in secondary care [10]. We have assumed that two 4 mg vials of zoledronate are used to make up a 5 mg dose (with approval of the STH Medicines Safety Committee). This reflects common practice in the NHS as the cost of the 5 mg vials of generic zoledronate is currently much higher than the cost of the 4 mg vials (£1.68 for 4 mg versus £122.50 for 5 mg) due to supply issues (personal communication, R Eastell, 21st Jan 2021). A breakdown of treatment costs per annum is provided in Supplementary Table S3.

Adverse events have been incorporated using the methods previously used by Davis et al. [7]. Costs and QALY losses associated with gastrointestinal adverse effects for oral bisphosphonates and QALY losses for flu-like symptoms for i.v. bisphosphonates have been incorporated as one-off adjustments at the start of treatment. Costs and QALY losses due to osteonecrosis of the jaw have also been applied to both oral and i.v. bisphosphonates but the impact of these are very small as the incidence of ONJ is assumed to be only 2 in 10,000 [7].

All model inputs are as reported by Davis et al. except where described otherwise [7]. Briefly, these include: risk of fracture in untreated patients; efficacy estimates; fracture-related costs; baseline utility values; fracture-related utility multipliers; all-cause mortality; and the likelihood of death or nursing home admission following fracture.

Costs are reported in GBP (£) at 2020 prices and future costs and QALYs have been discounted at 3.5% per annum in accordance with the National Institute for Health and Care Excellence (NICE) methods guide [11]. Fracture-related costs have been updated from those used by Davis et al. [7] by applying inflation indices to reflect changes in NHS unit costs [12].

Deterministic base-case and scenario analyses have been estimated by averaging outcomes over the simulated cohort of 50,000 patients when using midpoint parameter estimates. Probabilistic sensitivity analysis (PSA) has been conducted based on 1000 sets of parameter samples with the results for each set of parameter samples being taken as the average output over 50,000 patients. The proportions following each treatment pathway and the proportion having a second PINP test were sampled from beta distributions using the numbers observed in the cohort. The mean duration of treatment persistence for each treatment pathway in the DES was assumed to have a normal distribution with the mean and standard error calculated from the observational cohort. Drug costs and unit costs for PINP monitoring, zoledronate administration and DXA scans were assumed to be known precisely and were not varied in the PSA. All other inputs to the DES were sampled as previously described by Davis et al. [7]

3. Results

The baseline characteristics are shown in Table 1. From 906 patients (82.9% female), 588 patients (64.9%) were in the intention to monitor group (Group A) and 318 patients (35.1%) in the no intention to monitor group (Group B). The two groups did not differ for baseline characteristics, such as gender (82.8% of the population was female, *p* value 0.15) and age (mean of 71.3 years, *p* value 0.45), and for the main risk factors (57.9% of patients had a history of previous fractures, 16.4% were current smokers, 6.6% reported an alcohol intake above recommended limits of 14 units/week). There were no significant differences between the two groups regarding the baseline BMD assessment. The assessment of fracture risk using the FRAX tool, available for 888 patients, showed no differences between Group A and B in terms of 10-year probability of major osteoporotic fracture or hip fracture (*p* value 0.22 and 0.35, respectively).

Table 1
A selection of baseline characteristics of the population.

Baseline characteristics	Total	Group A	Group B	*P* value
No. of patients (%)	906	588 (64.9)	318 (35.1)	
Mean age (years)	71.3	71.2	71.7	0.45
Female No. (%)	750 (82.8)	479 (81.5)	271 (85.2)	0.15
Mean BMI (kg/m^2)	26.3 ± 4.9	26.2 ± 4.9	26.3 ± 4.9	0.88
Mean Lumbar BMD (g/cm^2)	0.810 ± 0.13	0.804 ± 0.13	0.820 ± 0.14	0.10
Mean Lumbar Spine T-score (SD)	−2.2 ± 1.14	−2.25 ± 1.11	−2.11 ± 1.12	0.10
Mean Hip BMD (g/cm^2)	0.724 ± 0.13	0.725 ± 0.13	0.722 ± 0.13	0.70
Mean Hip T-score (SD)	−1.84 ± 0.94	−1.83 ± 0.93	−1.87 ± 0.96	0.56
History of fractures	523/903 (57.9)	340 (58)	183 (57.7)	0.93
History of vertebral fractures	103/904 (11.4%)	60 (10.2%)	43 (13.6%)	0.13
History of hip fractures	210 (23.2%)	137 (23.3)	73 (23%)	0.91
Smoking risk	149 (16.4%)	97 (16.5%)	52 (16.4%)	0.95
Alcohol risk	60 (6.6%)	41 (7%)	19 (6%)	0.56
FRAX major (888 subjects)	19.5 ± 10.15	19.2 ± 9.96	20.04 ± 10.5	0.22
FRAX hip (888 subjects)	8.43 ± 8.22	8.25 ± 8	8.79 ± 8.6	T-test 0.35

3.1. Persistence to treatment

In the whole population, 611 patients (67.4%) started oral bisphosphonates as indicated by clinicians. We found a statistical difference between the two groups in the likelihood of starting the treatment: more patients ($n = 455$, 77.4%) belonging to Group A started oral treatment, while only 156 patients (49.1%) in the Group B started it (*p* value <0.001).

We had information about the presence or absence of gaps in prescriptions in 453 patients (339 in Group A and 114 in Group B). There were no significant differences in the presence or absence of gaps between the two groups: 87 patients in Group A and 27 patients in Group B had a gap (*p* value 0.674). Moreover, we calculated the duration of treatment, considering persistent the patients taking oral bisphosphonates for at least 5 years, and no differences were found between Group A and Group B (*p* value 0.92).

3.2. Changes in bone density during follow-up

In total, 369 patients had a follow-up scan (85.6% female). The changes in BMD were evaluated at 4–6 years from the baseline DXA scan. The mean percentage change for total hip BMD was significantly higher in Group A patients belonging to the intention to monitor group (an increase by 2.74% in Group A versus 0.42% in Group B; *p* value 0.003). There was a trend for a greater mean percentage increase for lumbar spine BMD in Group A [increase by 8.3% in Group A and by 6.2% in Group B (*p* value 0.06)]. Considering the change in BMD between patients who completed at least 5 years of treatment and those who did not (similar number of patients in each group), we found a significantly greater increase of lumbar spine BMD in the former group (11.3% vs 6.5%, *p* value 0.000); there was a similar trend for hip BMD changes, but the difference was not significant between the two groups (3.5% vs 2.0%, *p* value 0.1).

3.3. Incidence of new fractures during follow-up

Within the entire cohort, 369 patients (40.7%) had a follow-up DXA scan at the MBC within 4–6 years from baseline: 276 patients (46.9%) in Group A and 93 patients (29.2%) in Group B (*p* value 0.000). Hence, from their scan reports we verified the incidence of new fractures during the follow-up. Information from 366 out of 369 were available. A total of 93 new fractures occurred: 53 new vertebral fractures, 11 new hip fractures, 31 non-vertebral fractures. Even though there was a slightly higher incidence of new fractures in Group B, there was no significant difference between Group A and Group B in the incidence of total fractures ($n = 64$, 23.4% in Group A versus 29, 31.2% in Group B; *p* value 0.14), vertebral fractures (39, 14.3% in Group A vs 14, 15.1% in Group B; *p* value 0.86), or hip fractures (10, 3.7% in Group A vs 1, 1.1% in Group B; *p* value 0.21).

3.4. Changes in management

Monitoring PINP was associated with a significantly higher rate of management changes during the follow-up (125 patients, 21.6%, in Group A; 43 patients, 13.9%, Group B) (*p* value 0.005). There were no differences between the two groups in terms of referral to the MBC clinic (12 patients, 2% in the Group A versus 3 patients, 0.9% in the Group B; *p* value 0.22) or in changing to other oral medications (24 patients, 4.1% versus 11 patients, 3.5%; *p* value 0.64). Notably, the PINP change and level was not different in this group compared to patients who did not change management. Conversely, a significantly higher rate of patients in Group A changed to zoledronate treatment (96 patients, 16.3% in Group A versus 35 patients, 11% in Group B; *p* value 0.03). Almost half

of patients who changed to zoledronate (45.5%) received 3 infusions, which is the usually recommended dose for zoledronate treatment (mean of infusion 3.09, median 3.0 infusions), without any difference between monitored and not monitored group (p value 0.6).

3.5. PINP response

Only 38.6% (227 patients) had a follow-up PINP measurement performed at 4–9 months from the baseline PINP in Group A. Of these patients, 202 (89%) are considered responders because they reached at least one of the two targets (decrease by more than 10 μg/l from baseline or to below 35 μg/l). Only 25 patients (11%) were non responders. Poor responders had lower rate of BMD increase both at lumbar spine (6.7% vs 9.3% in responders) and at hip (1.5% vs 3.3%), but this observation was not significant (p value 0.30 for both sites). Furthermore, there was no difference in occurrence of new fractures between PINP responders (23.3%) and non-responders (16.7%) (p value 0.6). We were able to identify the reason underlying the poor response in 16 out of 25 patients: 2 of them were documented in GP reports as being poorly compliant to treatment; 7 patients did not start the treatment recommended and one died 10 months after starting it. In one case we found an increase in PINP levels from the baseline value to follow-up (from 123 μg/l to 212 μg/l) presumably due to a recent fracture (a distal radial fracture occurred 2 months before the second PINP measurement). Finally, five patients might be considered as late responder, since they reached the target of good response at a mean of 21.3 months from the baseline. We did not have access to clinical information to explain these results which may reflect a delay in initiating treatment or initial compliance issues which were successfully addressed.

3.6. Cost-effectiveness results

The deterministic base-case and scenario analyses are summarised in Table 2. It can be seen that although the intention to monitor strategy (Group A) is associated with additional costs (£28.28), it also results in additional QALYs gained (0.0041) as a greater proportion of patients started an antifracture treatment in the PINP monitoring arm (see Supplementary Table S1). The majority of the additional costs are related to the PINP monitoring itself (61%) which was estimated to cost £17.33 as 38.6% of the cohort received a second PINP test. The rest of the incremental costs are attributed to the additional treatment with i.v. bisphosphonates offered as a result of PINP monitoring. This is because the two treatment pathways that included treatment with i.v. bisphosphonates (pathways 2 and 3) resulted in additional costs compared to no treatment and these additional costs were not completely offset by the cost-savings achieved in those receiving only oral bisphosphonate treatment (see Supplementary Table S4). The incremental cost effectiveness ratio (ICER) for the intention to monitor strategy (Group A) relative to the no intention to monitor strategy (Group B) is £6096 in the deterministic base case analysis. As NICE usually considers interventions with an ICER under £20,000 to be cost-effective, this suggests that PINP monitoring has the potential to be cost-effective [11] in a UK NHS setting.

The spread of incremental costs and QALYs for the intention to monitor strategy (Group A) relative to the no intention to monitor strategy (Group B) based on the PSA are presented in Supplementary Fig. S3 with the average outputs summarised in Table 2. The intention to monitor strategy has a 99.9% likelihood of resulting in a QALY gain and a 19.3% likelihood of being cost-saving compared to the no intention to monitor strategy. The cost-effectiveness acceptability curve in Fig. S4 shows how the probability of the intention to monitor strategy being cost-effectiveness changes when a decision maker is willing to pay different amounts to achieve a gain of 1 QALY. PINP monitoring has probability of being cost-effective of 92.4% and 85.0% compared with no PINP monitoring if the decision maker is willing to pay £30,000 per QALY or £20,000 per QALY respectively. The mean ICER for the intention to monitor strategy versus the no intention to monitor strategy based on the PSA was £7,660 per QALY (see Table 2).

The scenario analyses conducted suggest that the conclusions are robust when making alternative plausible assumptions or using alternative data sources (see Table 2) as the ICERs remain under £20,000 per QALY in all of the scenarios presented. We assumed that NHS providers would use one 5 mg vial of generic zoledronate instead of using two 4 mg vials to make up the required dose and this increased the incremental cost to £43.41, resulting in an ICER of £10,600. PINP monitoring was cost saving compared to standard care without PINP monitoring after applying the lower unit cost for zoledronate administration used by Davis et al. [7,13]. We assumed that all of the patients in the intention to monitor group received a second PINP test and this increased the incremental cost for the intention to monitor group to £35.96 resulting in an ICER of £8780.

The proportion of patients with missing data on whether they started oral treatment was higher in the no intention to monitor group. In the base case analysis, it was assumed that patients with no information on whether they had started oral treatment had in fact not started oral treatment. In a scenario analysis, we made the opposite assumption, that they had in fact all started oral treatment. This increased the cost-savings and QALYs associated with treatment in both monitoring strategies. However, as this affected a greater proportion of patients in the no intention to monitor arm, this increased the incremental costs to £36.72 and reduced the incremental QALYs 0.0035. This resulted in an ICER of £10,478 per QALY for the intention to monitor strategy versus the no intention to monitor strategy.

In the base case scenario, we have assumed that patients are only offered a DXA at the end of their treatment which is the intention in the current Sheffield pathway that includes PINP monitoring. However, prior to PINP being available, it was routine practice for DXA to be offered at 2 years to monitor response to treatment. Therefore, the use of

Table 2
Base case and scenario analyses.

Scenario	Intention to monitor (Group A)		No intention to monitor (Group B)		Incremental		ICER
	Costs	QALY	Costs	QALY	Costs	QALY	
Base case	£67.32	0.0114	£39.04	0.0073	£28.28	0.0041	£6096
Administration costs for zoledronate and DXA costs from Davis et al. [7]	−£38.24[a]	0.0114	−£31.98[a]	0.0073	−£6.26	0.0041	Dominates[b]
All patients in the intention to monitor group receive a second PINP test	£74.99	0.0114	£39.04	0.0073	£35.96	0.0041	£8780
eMIT price for 5 mg vial of zoledronate	£114,34	0.0114	£70.93	0.0073	£43.41	0.0041	£10,600
Assume patients with missing data on oral bisphosphonate use all received oral bisphosphonates	£46.70	0.0129	£9.98	0.0094	£36.72	0.0035	£10,478
Assume PINP monitoring at 6 months replaces DXA at 2 years	£72.79	0.0114	£74.61	0.0073	−£1.82	0.0041	Dominates[b]
Base case PSA	£73.08	0.0110	£42.90	0.0070	£30.19	0.0039	£7660

[a] Negative costs for the strategies being compared occur when the treatment being offered to patients following that monitoring strategy is cost-saving compared to offering no treatment.

[b] Dominates means that the intention to monitor strategy reduces costs whilst increasing the QALYs gained compared to the no intention to monitor strategy.

PINP testing has the potential to reduce the use of DXA scans if these are currently used as a form of monitoring in NHS settings where PINP monitoring is not currently offered routinely. To explore this, we conducted a scenario analysis in which we assumed that the PINP testing at 6 months replaced a DXA scan that would otherwise occur at 2 years in all those started on a treatment following the baseline scan. Under these assumptions, the costs of monitoring are £72.79 in the PINP monitoring strategy and £74.61 when PINP monitoring is not available and DXA scans are used instead. Under these assumptions, the PINP monitoring strategy is cost-saving overall. This demonstrates that PINP monitoring has the potential to be more cost-effective if it replaces the routine use of DXA scans to monitor treatment response.

The estimate of net benefit when valuing a QALY at £30,000 provides information about how much additional cost could be incurred without increasing the ICER to above £30,000. In this case, PINP monitoring would achieve a net benefit of £94.58 compared to no monitoring based on the deterministic base case analysis. We can use this to assess whether our approach of excluding costs from other antifracture medications is likely to have biased the estimate of cost-effectiveness in a manner which would alter the conclusions. An additional 0.6% of patients received a medication other than zoledronate in the intention to monitor group (Group A) compared with the no intention to monitor group (Group B) (4.1% versus 3.5% of patients). Therefore, the additional medication received would need to have an average cost of £15,763 per patient whilst achieving no additional QALYs to push the ICER over £30,000 per QALY. As this is higher than the annual cost of either teriparatide or denosumab, it is unlikely that the exclusion of costs for other treatments from the analysis has significantly biased the conclusion. Similarly given that only an additional 1.1% of patients received a referral to the metabolic bone clinic in the intention to monitor group (2.0% versus 0.9% of patients), it is unlikely that our exclusion of these costs from the base case analysis will have significantly biased our conclusion that PINP monitoring is potentially cost-effective.

4. Discussion

Taking advantage of our experience of using BTMs for 20 years in our secondary care in Sheffield (UK), an algorithm has been developed to enable non-specialist practitioners to monitor anti-resorptive treatment delivered in primary care (Fig. 1). We made PINP our primary bone turnover marker in 2011. The decision to use PINP rather than CTX is because it is more easily handled and the absence of interference from feeding or circadian rhythm [14]. Thanks to this long experience in BTM monitoring, we designed the POSE (PINP and Osteoporosis in Sheffield Evaluation) study to establish the usefulness of the BTMs in monitoring osteoporosis treatment in a real-world setting. Lane and colleagues conducted a real-world data investigation on BTM use in a US setting. The authors determined that BTM testing was associated with a greater likelihood of making treatment decisions and of having a lower odds of fragility fracture [15].

In our study, we firstly evaluated whether the PINP measurement might be associated with better treatment persistence. Results supported a higher likelihood of starting treatment in the monitored group (77.4% in Group A versus 49.1% in Group B, p value 0.000). The IOF/ECTS Working Group [5] recommendations for the screening of adherence to oral bisphosphonates indicate that three months after prescription is early enough to assess how patients accept and tolerate the treatment; it also covers the critical period of primary non-adherence, when patients may have discontinued or never have started the treatment [16]. Medication-taking behavior encompasses two components: compliance or adherence (defined as percentage of doses taken as prescribed, usually using an arbitrary cut-off set at 80%) and persistence (defined as cumulative time on treatment from initiation to discontinuation, without exceeding a permissible gap, generally 30 to 120 days) [17]. Treatment for osteoporosis is a long-term treatment and persistence rates gradually decrease over time. The highest rate of discontinuation is often seen within the first year and the most common causes of non-persistence are adverse effects, poor health literacy and costs. Both compliance and persistence seem to be higher with monthly regimens than weekly ones [18]. In our study, we found no significant difference in treatment persistence between patients in the intention to monitor and the no intention to monitor groups, whether considering the presence of gap or the treatment duration. Contrasting evidence is available on the effectiveness of measurement of BTMs to enhance persistence. Roux et al. similarly failed to demonstrate that CTX monitoring had an impact on persistence with Ibandronate therapy, nor did they observe that feedback of a positive monitoring result had more impact than a negative message [19]. Providing NTX response information in association with a program of continuing education was shown to be helpful and seems to be making patients more aware about the importance of taking treatment. However, when comparing persistence, no differences were found between the groups receiving and not receiving information [20].

During the follow-up, more patients in Group A (p value 0.0001) had a follow-up BMD measurement at 4–6 years from baseline: we can speculate it might be due to a better adherence to the Sheffield algorithm and a stricter clinical follow-up provided by GPs. Among this cohort of patients, about 25% had new fractures during the follow-up. The BMD improvement during the follow-up was higher in the monitored group of patients, although it reaches significance only for total hip BMD (p value 0.003). In terms of lumbar spine BMD, we did not find any differences and this could be due to artefactual increases which we would expect to be similar in both groups; lumbar spine usually develops degenerative changes over the years, that lead to a false increase of BMD [21].

The Sheffield PINP monitoring algorithm requires further investigation if the PINP decrease at 6 months is not below the target expected. In these cases, GPs should reassess the compliance, investigate if adverse events occurred and consider causes of poor response such as impaired absorption or secondary osteoporosis. Another approach is to refer the patient to the MBC or to advise a change of treatment. In our study, more patients in the monitored group changed management (p value 0.005) including switching to zoledronate infusions (p value 0.03). It suggests that monitoring PINP during the first months of treatment might help clinicians to identify patients with poor response to oral treatment and refer them to secondary care, with the chance to receive intravenous therapies. The zoledronate persistence in our study (at 3 years 45.5% of patients) is consistent with persistence at 3 years ranging from 20 to 54% (median 35.8%) reported in literature [22].

Finally, the evaluation of the PINP measurement pathway showed that 38.6% of patients correctly followed the Sheffield algorithm performing a follow-up PINP measurement at 4–9 months from the baseline with a response rate of 89%. This value is lower than we expected but this might be because we were strict with our follow-up window. A reduction of bone turnover markers exceeding LSC has been associated with a lower risk of vertebral and nonvertebral fractures [23], with a stronger relationship with the bone formation than bone resorption markers [24]. However, we found no differences in the occurrence of new fractures or in BMD changes in patients with a poor response to PINP in comparison with those who met the target. That was presumably due to the small numbers. The lack of PINP response in 11% of patients was clearly explained in those patients who did not start the recommended treatment. Adherence to treatment is positively correlated with BTM changes [23], so a poor response is expected in the two patients reported as poorly compliant by GPs. In one case, we reported a new fracture occurred before the follow-up PINP assessment, rendering the result uninterpretable as fracture healing causes a rise of BTM levels that can remain elevated up to one year after a fracture [25]. No other underlying causes of secondary osteoporosis were identified among the non-responders.

Our study has some limitations. These are mainly related to the retrospective nature of the study and to the real-world setting. Missing data due to incomplete databases are common in this kind of study

study. In addition, finding information about what was done in primary care from the secondary care records was not always possible and accessible, since data-sharing is not universal. In particular, information like the timing of the treatment (*ie.* when it is started or stopped), reasons for early discontinuation, percentage of administered tablets (that might help to identify the compliance) was difficult to assess. In approximately one third of patients we did not have access to the GP records. Another limitation is that new vertebral fractures are more likely to have been identified in Group A as a higher proportion had follow-up DXA and most will have had VFA at the same time as this is routine in our clinical practice for all women over 65, men over 70 and in younger patients meeting criteria such as steroid therapy or prior vertebral fracture [26]. Furthermore, the development of the monitoring algorithm and the availability of PINP measurement pre-dated the baseline data in this study by just a few months: thus, at that time GPs were still used to monitor anti-osteoporosis treatment using serial DXA scan rather than BTMs. This may explain why many patients were not monitored using PINP and why many of those with a baseline PINP measurement did not have a follow-up measurement. Finally, there was no information on adherence. The size of the population is one of our strengths and as the patients were consecutively identified they are representative of the local primary care referral population; however, the small number of fractures is a limitation. Furthermore, the real-world setting itself is another strength because it provides the actual usefulness of monitoring PINP in primary care.

Based on our analysis, the intention to monitor strategy (Group A) has an ICER of £7660 compared to the no intention to monitor strategy (Group B) and has a high probability of being cost-effective at the £20,000 to £30,000 per QALY threshold applied by NICE. These findings were relatively robust when plausible alternative data sources and assumptions were explored in the scenario analyses. In some scenarios the intention to monitor strategy had a lower cost and higher QALY gains than the no intention to monitor strategy. However, there are some limitations that should be considered when interpreting these findings.

This analysis is based on an observational study in which patients were separated into the intention to monitor group and the no intention to monitor group according to whether they received a PINP test around the time of their baseline DXA scan. This is therefore not a randomised comparison and there may be differences between the patients in the groups that were not detected in the comparison of baseline characteristics. Furthermore, it may be that the clinicians who took up the opportunity for PINP monitoring were managing their patient's fracture risk more pro-actively than those that did not and that these differences were being driven by factors other than the availability of the PINP monitoring, such as the importance the GP placed on fracture prevention.

The cohort was based on data collected retrospectively. Thus, it was not possible to determine exactly whether and when each patient was started on bisphosphonates or which medications were prescribed other than oral bisphosphonates and i.v. zoledronate. It is unlikely that many patients were treated with other anti-osteoporosis treatments such as denosumab. Therefore, the economic analysis has made several simplifying assumptions to allocate patients to treatment pathways according to the data available. We have attempted to explore whether the assumptions related to the handling of missing data are likely to have significantly biased the analysis by exploring the impact of making alternative assumptions. However, there is still some uncertainty as to whether the conclusions would have been the same if complete data on the treatments received and the duration of treatment had been available for all patients.

The analysis assumes that the higher rate of DXA associated with PINP monitoring is explained by the higher rate of patients starting treatment who are then assumed to go on to receive a DXA scan at the end of treatment. There was a 17.7% increase observed in the proportion of patients having a follow-up DXA in the intention to monitor arm in the POSE cohort (Group A) (46.9% versus 29.2%, $p < 0.001$). However, this difference is smaller than the 29.6% difference in the proportion of patients receiving some form of antifracture medication (see Table 1). This means that the difference in use of follow-up DXAs between the two groups is not fully explained by the assumption that DXA is repeated only at the end of treatment.

This observational cohort could not be used to determine whether the use of DXA scans was reduced by the introduction of PINP monitoring as the switch from monitoring with DXA scans to monitoring with PINP testing had already been made in the Sheffield pathway a few months before the data collection for this study began. However, we have attempted to explore the potential impact on cost-effectiveness if PINP monitoring were used to replace DXA in a scenario analysis. This suggests that PINP monitoring has the potential to be cost-saving whilst also increasing QALYs gained if it is used to replace a policy of routinely offering DXA scans to assess response to treatment.

CRediT authorship contribution statement

Study design: SD, BA, NP, RE. Data collection: CMW, LM. Data analysis and interpretations: all authors. Drafting manuscript: LM. Revising manuscript: all authors. Approval of final manuscript: all authors. All the authors take responsibility for the integrity of the data analysis.

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BA reports grants and personal fees from UCB, personal fees from Amgen, grants from Novartis, grants and personal fees from Pharmacosmos, grants and personal fees from Kyowa Kirin, personal fees for Gedeon Richter outside the submitted work. BA also serves on the Novo Nordisk Foundation Grants Committee on Endocrinology and Metabolism.

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Appendix A. Supplementary data

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