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# Cost-effectiveness of zoledronic acid and strontium-89 as bone protecting treatments in addition to chemotherapy in patients with metastatic castrate-refractory prostate cancer: results from the TRAPEZE trial (ISRCTN 12808747).

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**Running head:** Cost-effectiveness of ZA and Sr89 in castrate-refractory prostate cancer.

## Abstract

**Objectives:** To evaluate the cost-effectiveness of adding zoledronic acid (ZA) or strontium-89 (Sr89) to standard docetaxel chemotherapy for patients with castrate-refractory prostate cancer (CRPC).

**Patients and methods:** Data on resource use and quality of life for 707 patients collected prospectively in the TRAPEZE 2x2 factorial randomised trial (ISRCTN 12808747) were used to assess the cost-effectiveness of i) zoledronic acid versus no zoledronic acid (ZA vs. no ZA), and ii) strontium-89 versus no strontium-89 (Sr89 vs. no Sr89). Costs were estimated from the perspective of the NHS and included expenditures for trial treatments, concomitant medications and use of related hospital and primary care services. QALYs were calculated according to patients' responses to the generic EuroQol EQ-5D-3L instrument. Results are expressed as incremental cost-effectiveness ratios (ICER) and cost-effectiveness acceptability curves.

**Results:** The per-patient cost for ZA was £12,667, £251 higher than the equivalent cost in the no ZA group. Patients in the ZA group experienced on average 0.03 QALYs more than their counterparts in no ZA. The incremental cost-effectiveness ratio (ICER) for this comparison was £8,005. Sr89 was associated with a cost of £13,230, £1,365 higher than no Sr89, and a gain of 0.08 QALYs compared to no Sr89. The ICER for Sr89 was £16,884. The probabilities of ZA and Sr89 being cost-effective were 0.64 and 0.60, respectively.

**Conclusions:** The addition of bone-targeting treatments to standard chemotherapy led to a small improvement in QALYs for a modest increase in cost (or cost-savings). ZA and Sr89

resulted in ICERs below conventional willingness-to-pay per QALY thresholds, suggesting that their addition to chemotherapy may represent a cost-effective use of resources.

**Keywords:** castrate-refractory prostate cancer; cost-effectiveness analysis; quality of ilife; bone protecting treatments; zoledronic acid; strontium-89

## Introduction

Prostate cancer is one of the commonest types of cancer and a major health problem around the world. In 2012, more than 1.1 million men were diagnosed with prostate cancer making this the second most common male cancer worldwide, accounting for approximately 15% of all newly diagnosed male cancers. [1] In the UK, prostate cancer is the commonest form of cancer, with approximately 42,000 men being diagnosed with the disease and almost 11,000 men dying from it annually. [2]

Prostate cancer typically presents as local disease, but a significant proportion of patients progress despite initial treatment. Hormone therapy has been the main treatment for relapsed prostate cancer, [3] leading to responses typically lasting for 12 to 24 months. The period after failure of initial androgen deprivation therapy is now termed castrate-resistant prostate cancer (CRPC). [4] Following two landmark trials, chemotherapy with docetaxel and prednisolone (DP) is considered the bedrock of therapy for metastatic CRPC. [5, 6]

In patients with metastatic disease, the commonest site of spread is bone. Two treatments approved for bone disease are zoledronic acid [7, 8] (ZA) and strontium-89 [9, 10] (Sr89). A pre-docetaxel era trial combined chemotherapy with Sr89 in a small randomised trial and suggested a survival advantage in patients allocated to Sr89. [11] ZA is approved on the basis of reductions in skeletal-related events (SRE), a composite endpoint including symptomatic fractures, surgeries and radiotherapy to bone.

There is considerable uncertainty as to whether the cost of adding bone-protecting treatments, such as ZA or Sr89, to standard chemotherapy would be warranted by improved quality of life (QoL) and reduced use of health care resources, possibly due to fewer

skeletal-related events. This question is particularly pertinent as zoledronic acid is now available as a generic product, at a considerably lower price than its branded counterpart.

Given this, we sought to assess the cost effectiveness of adding bone-protecting treatments to docetaxel chemotherapy for patients with castrate-refractory prostate cancer (CRPC), using prospectively collected data from the TRAPEZE 2x2 factorial randomised controlled trial (ISRCTN 12808747). Two relevant comparisons were explored in the trial: i) zoledronic acid in addition to standard chemotherapy versus no zoledronic acid (ZA vs. no ZA), and ii) strontium-89 in addition to standard chemotherapy versus no strontium-89 (Sr89 vs. no Sr89).

## Patients and methods

The TRAPEZE trial design is described in detail elsewhere [12, 13]. Briefly, this was a randomized open label phase III study using a 2x2 factorial design aiming to compare ZA vs. no ZA (stratified for Sr89) and Sr89 vs. no Sr89 (stratified for ZA). The trial recruited 757 patients with progressive metastatic CRPC according to the following eligibility criteria: age ≥ 18, ECOG score ≤ 2, and adequate haematological, renal and hepatic function. Participants were randomised to one of four arms: i) DP arm: docetaxel 75mg/m2 3-weekly and oral prednisolone 10 mg daily for up to 10 cycles; ii) DP+ZA arm: docetaxel and prednisolone plus zoledronic acid 4mg three weekly during chemotherapy then 4 weekly until disease progression; iii) DP+Sr89 arm: docetaxel and prednisolone for six cycles, strontium-89 150 MBq then further docetaxel and prednisolone up to total of 10 cycles; iv) DP+ZA+Sr89 arm: docetaxel and prednisolone plus both strontium-89 and zoledronic acid as above. Ethical

approval was received from the Multicentre Research Ethics Committee and regulatory approval was granted by the UK Medicines and Healthcare Regulatory Agency.

The primary outcome of the clinical analysis was clinical progression-free survival (CPFS), defined as the number of days from randomisation to the first occurrence of a symptomatic SRE, pain progression or death. The main outcome of the cost-effectiveness analysis is cost per quality-adjusted life year (QALY). Responses to EQ-5D needed for calculating QALYs and, thereby, cost-effectiveness in this trial were available for 707 (93%) of the 757 patients. This was a representative subgroup of the trial patients (Table S1). Patient characteristics are given in Table 1.

***Resource use and cost***

Data on health care resource use were collected prospectively through case report forms (CRF) and patient-completed questionnaires. Relevant resource use fell under three main categories: i) trial treatments; ii) concomitant treatments, and iii) use of other related hospital and primary care services. The cost of trial treatments was calculated according to patient-specific doses and number of treatment cycles provided, taking into account the cost of drug administration. The cost of care or medications provided concomitantly with trial treatment (radiotherapy, abiraterone, cabazitaxel, mitoxantrone, blood transfusions, additional docetaxel, strontium-89, zoledronic acid and surgical procedures) was obtained by weighting their respective use recorded in CRFs by unit costs available from national sources (Table 1) [14-17]. Outpatient appointments, inpatient stay and general practitioner visits were drawn from CRFs, while post-treatment hospital stay and visits were obtained from patient-completed questionnaires. Questionnaire data were missing for 126 patients and were imputed using multiple imputation by chained equations [18].

***Quality of life and QALYs***

QALY scores were derived by translating responses to the EQ-5D-3L health status instrument [19] into preference-based (utility) scores using a standard value set [20]. EQ-5D was collected three weekly during treatment, then monthly for 3 months and 3 monthly until death. QALYs were calculated as the area under the curve connecting utility scores available at different time points. For patients who were known to have died, a utility of zero was assigned on the date of death [21]. For patients still alive at the time of analysis, their last known EQ-5D-3L score was carried forward to the date last seen.

***Cost-effectiveness analysis***

Analyses were conducted from the perspective of the National Health System in the UK. In line with recommendations, costs and benefits accruing beyond 12 months were discounted at a rate of 3.5% per year [22]. A total cost and a total number of QALYs were calculated for each patient, with 95% confidence intervals around mean values obtained through 1000 bias corrected and accelerated (BCa) bootstrap replications [23, 24]. Given the short expected survival time of metastatic CRPC patients and the long-term follow-up of patients in the trial, lifetime costs and effects were largely observed and so extrapolation beyond the trial was unnecessary. In the comparison between ZA and no ZA, the main analysis was based on the fact that, as of 2013, zoledronic acid has been available as a generic product, at a price significantly lower than its branded counterparts. Additional analyses were conducted on the basis of the proprietary product.

Differences in mean total costs and QALYs between the compared options were presented as incremental cost-effectiveness ratios (ICERs), a measure reflecting the additional cost associated with a gain of an additional QALY [25]. To account for uncertainty in the results,

nonparametric bootstrapping was used to replicate the joint distribution of the differences in cost and QALYs [26]. This generated 5000 paired estimates of incremental costs and QALYs, which were subsequently used to derive cost-effectiveness acceptability curves (CEACs) [27]. CEACs show the probability of each option being cost-effective across a range of possible values of willingness to pay (ceiling ratio) for an additional QALY [28]. The impact of alternative assumptions and uncertain values on the results was explored in additional sensitivity analyses.

## Results

### *Comparison of ZA vs no ZA*

Cost by resource use category, total costs and total QALYs for the comparison between ZA and no ZA are given in (Table 2). The most substantial difference in costs was due to the use of zoledronic acid itself provided as protocol and follow-up treatment in the ZA group. With the exception of zoledronic acid, patients in the ZA group presented lower use of additional care and medications. Notably, there were differences in the use of radiotherapy and surgery, reflective of the fact that patients in the ZA group experienced fewer SREs. The difference in total costs between ZA and no ZA was £251 (BCa 95% CIs: -£1099 to £1602); this difference was contingent on the acquisition cost of zoledronic acid. In relation to health benefits, patients in the ZA group had an average of 0.91 QALYs, reflecting a gain of 0.03 QALYs (BCa 95% CI: -0.07 to 0.13) over their counterparts in the no ZA group.

Combining differences in costs and QALYs resulted in an ICER of £8005 per QALY. At the commonly-cited lower willingness-to-pay ratio of £20,000 per QALY in the UK [22, 29-33], the probability of ZA being cost-effective is 0.64 (Figure 1). For prices of zoledronic acid

between £0 and £31, the total per-patient cost of ZA is lower than that of no ZA and, given the fact that ZA is associated with a slight increase in QALYs, this treatment option dominates its comparator. For prices between £31 and £98, ZA results in ICERs up to £20,000 per QALY, and it is thus cost-effective at this willingness-to-pay value.

Most of the alternative assumptions explored in additional sensitivity analyses (e.g. different prices of concomitant medications, no discounting etc.) had a small, proportional effect on the additional cost and benefits of each treatment option, and, thus, they had a minimal impact on the resulting ICER (Table S2). The only exception was the adjustment of QALYs for baseline imbalances in EQ-5D scores, which resulted in a very small, non-significant difference in QALYs in favour of no ZA (0.0006 QALYs, CIs: -0.096 to 0.094). For zoledronic acid prices up to £28, ZA is less costly and less effective, but overall more cost-effective than no ZA (at £20,000 per QALY foregone), and it is more costly and less effective (i.e. dominated) above this price (Figure S1).

***Comparison of Sr89 vs no Sr89***

The most prominent difference in mean costs between the Sr89 and no Sr89 groups was due to the use of strontium-89 itself. Apart from the higher cost for strontium-89, the Sr89 group was associated with greater cost for docetaxel and zoledronic acid given as protocol treatments, higher cost for cabazitaxel and docetaxel provided as concomitant medications, and increased cost due to surgeries. On the other hand, the Sr89 group was associated with fewer radiotherapies, lower use of abiraterone, zoledronic acid and strontium-89 as concomitant medications, and fewer inpatient days, outpatient appointments and GP visits (Table 3). The analysis showed mean total costs per person of £13,230 and £11,865 for Sr89 and no Sr89 respectively, resulting in a mean difference of £1365 (BCa 95% CIs: -£12 to

£2,742). For the comparison between Sr89 vs no Sr89, patients who received Sr89 showed a gain of 0.08 QALYs (BCa 95% CIs: -0.019 to 0.181) over those in the no Sr89 group.

Overall, Sr89 was associated with a higher total per-patient cost and a greater mean number of QALYs compared to no Sr89. Given these differences, the point estimate ICER for Sr89 was calculated at £16,884 per additional QALY. At a willingness-to-pay value of £20,000 for an additional QALY, the probability that Sr89 is cost-effective is 0.6 (Figure 2). The ICER for Sr89 remains bellow £20,000 per QALY for prices of strontium-89 up to £2120.

Most of the alternative scenarios explored in sensitivity analyses had a limited impact on the magnitude of the results and did not change the baseline conclusion for this comparison (Table S2). An exception was the analysis using different prices for strontium-89: a lower price of strontium-89 gives an ICER of £13,182 per QALY, whereas a higher price resulted in an ICER of £20,585 per QALY.

## Discussion

This study uses patient level data collected in the TRAPEZE trial to determine whether the addition of ZA or Sr89 bone-protecting therapies to standard chemotherapy represents a cost-effective use of healthcare resources.

The comparison between ZA and no ZA showed ZA to be associated with a small additional cost for a slight improvement in QALYs. This additional cost was relatively modest, owing to the low additional cost for zoledronic acid and the fact that this cost was largely counterbalanced by reduced use of other healthcare resources (e.g. fewer radiotherapies and surgeries). Prevention of serious events such as fracture, surgery and cord compression is seen as a desirable outcome for the NHS [34]; therefore, a predictable, outpatient therapy

with modest net acquisition costs may be attractive to providers if it prevents emergency, unpredictable visits. In the likely case that the NHS pay less than £31 for a dose of zoledronic acid, ZA is the dominant option, being less costly and more effective than no ZA.

The magnitude of the additional cost in the ZA group is to a great extent dependent on the acquisition cost of zoledronic acid. Since 2013, zoledronic acid is available as a generic product, at a price markedly lower than the equivalent proprietary products (Zometa® and Aclasta®). Given the average price paid by NHS hospitals for zoledronic acid in the UK, the additional cost of ZA was low, at £251, resulting in an attractive ICER of about £8,000 per QALY. In the likely case that the NHS pay less than £31 for a dose of zoledronic acid, ZA is the dominant option (i.e. less costly and more effective, in terms of QALYs, than no ZA).

The Sr89 group was associated with an increase in cost and an improvement in QALYs, which translated into an ICER of £16,900 per QALY. However, these results will need to be seen in light of the fact that a number of new treatments licenced in the last few years have now emerged, including abiraterone, enzalutamide, cabazitaxel and, of particular relevance to this study, radium-223.

For both the comparison between ZA vs no ZA and Sr89 vs no Sr89, the calculated confidence intervals of the differences in QALYs overlapped zero, suggesting that the observed improvements in QALYs are not statistically significant. However, given the fact that the TRAPEZE trial was not powered to detect statistically significant differences in QALYs, the observed results should not be interpreted as conclusive evidence of presence or absence of a significant difference. In line with recommendations, the interpretation of the

results is based on the outcome of the incremental cost-effectiveness ratios and the uncertainty surrounding them [25, 35].

To our knowledge, this is the first economic evaluation based on prospectively collected data aiming to assess the cost-effectiveness of providing CRPC patients with ZA and Sr89 in addition to standard chemotherapy. A major strength of this study lies in the fact that data were obtained from a large pragmatic randomised controlled trial. In line with guidance in conducting economic evaluations, costs were estimated by weighting prospectively-collected patient-level resource use by unit costs drawn from national sources, health benefits were measured using a widely used preference-based measure, and analyses of the collected data were performed using recommended statistical methods [24, 36-38]. While the analysis was carried out from the perspective of the NHS in the UK, the fact that the care pathway for CRPC is similar across developed countries makes the findings pertinent to other health care systems.

Despite this, the study presents certain methodological challenges. First, ZA appeared to have a minimal effect on QoL, which did not tally with the marked change in the number and severity of SREs. Given that events such as pain leading to radiotherapy, fracture and spinal cord compression must certainly impair QoL, it is possible that temporary drops in QoL due to unpredictable SREs may have not been captured. This may be explained by the fact that EQ-5D forms are typically completed at predetermined points after randomisation, which are likely to fall either before SREs or after problems are resolved. Failure to capture temporary declines in QoL due to SREs indirectly penalises groups associated with fewer SREs—in this case, the ZA group. Secondly, similarly to all trials, prospectively collected data are bound to be incomplete. In particular, final terminal phase SREs, resource use and

benefits are difficult to capture, as patients are generally less likely to attend trial clinics in that period [39, 40]. Last, while the trial protocol made provisions for six cycles of docetaxel chemotherapy plus an additional four cycles 'off study', NICE in the UK recommended that up to 10 cycles of docetaxel chemotherapy should be administered in one treatment block. Given the intended pragmatic nature of this trial, adopting the NICE recommendation ensured that treatment arms reflected the true 'standard of care'. Owing to the fact that docetaxel chemotherapy was provided across all treatment groups, this change is not expected to impact on a particular treatment group over another.

Further research in the area would be valuable. Despite the patient-level evidence obtained from the trial, more detailed estimates of QoL associated with SREs and use of healthcare resources would be useful. The latter is typically accessible via the Hospital Episode Statistics (HES) database, which contains details of all admissions, outpatient appointments and emergency attendances at NHS hospitals [41]. Further analyses using HES will give the opportunity to corroborate the study findings. In addition, it would be interesting to obtain insights into the clinical effectiveness and cost-effectiveness of both ZA and Sr89 as compared to neither treatment. While the TRAPEZE trial was not designed to investigate such comparisons, this could be pursued in a future study specifically designed to assess the particular treatment options.

In conclusion, findings suggest that the addition of bone targeting treatments to standard chemotherapy lead to a small positive change in QALYs for a small additional cost (or cost-savings), resulting in an ICER below the threshold of £20,000 per QALY. These cost-effectiveness results, coupled with the treatments' positive impact on SRE prevention,

suggest that supplementation of chemotherapy with bone-protecting treatments is likely to represent a cost-effective use of the available health care resources.

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## References


1. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2014. Estimated cancer incidence, mortality and prevalence worldwide in 2012. Lyon, France: International Agency for Research on Cancer;2014.

2. Prostate cancer Key Facts. 2014. http://publications.cancerresearchuk.org/downloads/Product/CS_KF_PROSTATE.pdf. Accessed October 1, 2014.

3. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol. Jul 2002;168(1):9-12.

4. Scher HI, Halabi S, Tannock I, et al. Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-1159.

5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. Oct 7 2004;351(15):1502-1512.

6. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-1520.

7. Saad F, Gleason DM, Murray R, et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. J Natl Cancer Inst. 2002;94(19):1458-1468.

8. Saad F, Gleason DM, Murray R, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J Natl Cancer Inst. 2004;96(11):879-882.

9. Bolger JJ, Dearnaley DP, Kirk D, et al. Strontium-89 (Metastron) versus external beam radiotherapy in patients with painful bone metastases secondary to prostatic cancer: preliminary report of a multicenter trial. UK Metastron Investigators Group. Semin Oncol. 1993;20(3 Suppl 2):32-33.

10. Quilty PM, Kirk D, Bolger JJ, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. Radiother Oncol. 1994;31(1):33-40.

11. Lennox AS, Osman LM, Reiter E, et al. Cost effectiveness of computer tailored and non-tailored smoking cessation letters in general practice: randomised controlled trial. Brit Med J. 2001;322(7299):1396.

12. James ND, Pirrie S, Pope A, et al. TRAPEZE: A randomised controlled trial of the clinical and cost effectiveness of chemotherapy with zoledronic acid, strontium-89 or both, in men with bony metastatic castrate refractory prostate cancer. Health Technol Assess 2015. In press.

13. James ND, Pirrie S, Barton D, Billingham L. Clinical outcomes in patients with castrate-refractory prostate cancer (CRPC) metastatic to bone randomized in the factorial TRAPEZE trial to docetaxel (D) with strontium-89 (Sr89), zoledronic acid (ZA), neither, or both (ISRCTN 12808747). J Clin Oncol 2013: 31 (suppl; abstr LBA5000).

14. British Medical Association. British National Formulary. London: BNA and RPS; 2014.

15. Curtis L. Unit Cost of Health and Social Care. Personal Social Services Research Unit. http://www.pssru.ac.uk/project-pages/unit-costs/2014/. Accessed July 19, 2014.

16. Department of Health. National Schedule of Reference Costs 2013 to 2014. https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014. Accessed July 21, 2014.

17. NHS Commercial Medicines Unit. Electronic Market Information Tool. 2014; http://cmu.dh.gov.uk/electronic-market-information-tool-emit/. Accessed October 17, 2014

18. Lee KJ, Carlin JB. Multiple imputation for missing data: fully conditional specification versus multivariate normal imputation. Am J Epidemiol. 2010;171(5):624-632.

19. Brooks R. EuroQol: the current state of play. Health Policy. 1996;37(1):53-72.

20. Dolan P. Modeling valuations for EuroQol health states. Med Care. 1997;35(11):1095-1108.

21. Billingham LJ, Abrams KR, Jones DR. Methods for the analysis of quality-of-life and survival data in health technology assessment. Health Technol Assess. 1999;3(10):1-152.

22. NICE. Guide to the methods of technology appraisal 2013. 2013. http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf. Accessed September 14, 2014.

23. Barber J, Thompson S. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. Stats Med. 2000;19(23):3219-3236.

24. Glick HA, Jalpa DA, Sonnad SS, Polsky D. Economic evaluation in clinical trials. Oxford: Oxford University Press; 2007.

25. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press; 2005.

26. Glick HA, Briggs AH, Polsky D. Quantifying stochastic uncertainty and presenting results of cost-effectiveness analyses. Expert Rev Pharmacoecon Outcomes Res. 2001;1(1):25-36.

27. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. Health Econ. 1994;3(5):309-319.

28. Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). Value Health. 2008;11(5):886-897.

29. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ. 2004;13(5):437-452.

30. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ. 1992;146(4):473-481.

31. Pritchard C. Overseas approaches to decision making. In: Towse A, Pritchard C, Devlin N, eds. Cost-effectiveness thresholds. Economic and Ethical Issues. London: King's Fund and Office of Health Economics; 2002.

32. Weinstein MC. How much are Americans willing to pay for a quality-adjusted life year? Med care. Apr 2008;46(4):343-345.

33. Bae YHJ, Mullins CD. Do value thresholds for oncology drugs differ from nononcology drugs? J Manag Care Pharm. 2014;20(11):1086-1092.

34. Department of Health. NHS 2010–2015: from good to great. Preventative, people-centred, productive. 2009. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/228885/7775.pdf. Accessed February 14, 2015.

35. Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S. Applied methods of cost-effectiveness analysis in healthcare: OUP Oxford, 2011

36. Ramsey S, Willke R, Briggs A, et al. Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials: The ISPOR RCT-CEA Task Force Report. Value Health. 2005;8(5):521-533.

37. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing... presumed at random: cost-analysis of incomplete data. Health Econ. 2003;12(5):377-392.

38. Andronis L, Barton P, Bryan S. Sensitivity analysis in economic evaluation: an audit of NICE current practice and a review of its use and value in decision-making. Health Technol Assess. 2009;13(29):iii, ix-61.

39. McMillan SC, Weitzner MA. Methodologic issues in collecting data from debilitated patients with cancer near the end of life. Oncol Nurs Forum. 2003;30(1):123-129.

40. Molenberghs G, Kenward M. Missing data in clinical studies. Vol 61: John Wiley & Sons; 2007.

41. Hospital Episode Statistics database 2015. http://www.hscic.gov.uk/hes. Accessed May 15, 2015.

## Legends to illustrations

Figure 1. Cost Effectiveness Acceptability Curve showing the probability of ZA being cost-effective at different values of willingness to pay per additional QALY

Figure 2. Cost Effectiveness Acceptability Curve showing the probability of Sr89 being cost-effective at different values of willingness to pay per additional QALY.

Figure S1. Graph showing Incremental Cost Effectiveness Ratio for ZA vs no ZA at different prices of zoledronic acid, after adjusting for baseline imbalances in EQ-5D-3L

## Tables and legends

Table 1. Unit cost prices and sources

Table 2. Mean per-patient cost and QALYs for ZA vs no ZA

Table 3. Mean per-patient cost and QALYS for Sr89 vs no Sr89

Table S1. Summary characteristics of participants included in the economic evaluation (n=707) and all study participants (n=757)

Table S2. Results of sensitivity analyses for ZA vs no ZA and Sr89 vs no Sr89.

## Tables

**Table 1. Unit cost prices and sources**

| Item | Cost | Source |
|---|---|---|
| Docetaxel | £155 (for 1ml vial (20mg)) | British National Formulary[14] |
| Prednisolone | £0.64 per day | British National Formulary[14] |
| Zoledronic acid | £58 (for 4mg) | NHS Commercial Medicines Unit[17] |
| Strontium-89 | £1710 (per fraction of 150mbq) | Nuclear Medicine Department, University Hospital Birmingham. |
| Abiraterone | £98 per day | British National Formulary[14] |
| Cabazitaxel | £3696 per cycle | British National Formulary[14] |
| Mitoxantrone | £100 per cycle | British National Formulary[14] |
| Radiotherapy | £813 cost of radiotherapy preparation plus £118 cost of radiotherapy fraction | NHS Reference Costs[16] |
| Blood | £123 per unit plus intravenous cannula (£1) and blood giving set (£4) | NHS Blood and Transplant |
| Administration of DP, ZA (standalone), mitoxandrone | £245 | NHS Reference Cost[16] |
| Administration cabazitaxel | £144 | NHS Reference Cost[16] |
| Administration of Sr89 | £443 | Nuclear Medicine Department, University Hospital Birmingham |
| Blood transfusion | £172 | NHS Reference Cost[16] |
| Decompression for spinal cord compression | £9,573 | NHS Reference Cost[16] |
| Laminectomy | £6,893 | NHS Reference Cost[16] |
| Intramedullary nailing | £4,995 | NHS Reference Cost[16] |
| Hip replacement | £8,038 | NHS Reference Cost[16] |
| Fracture | £3,888 | NHS Reference Cost[16] |
| Spinal cord compression | £7,816 | NHS Reference Cost[16] |
| Inpatient stay | £680 | NHS Reference Cost[16] |
| Outpatient appointment | £135 | Personal Social Services Research Unit[15] |
| GP consultation | £63 | Personal Social Services Research Unit[15] |

**Table 2. Mean per-patient cost and QALYs for ZA vs no ZA**

| | ZA (n=350) | | No ZA (n=357) | | Difference (ZA vs. no ZA) | | |
|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | ***Mean difference*** | ***Lower 95% CI**** | ***Upper 95% CI**** |
| ***Trial treatment*** | | | | | | | |
| *Docetaxel + prednisolone* | *£2,502* | *£760* | *£2,441* | *£749* | *£60* | *-£49* | *£169* |
| *Zoledronic acid* | *£346* | *£151* | *£0* | *£0* | *£346* | *£330* | *£361* |
| *Strontium-89* | *£769* | *£1,033* | *£724* | *£1,018* | *£45* | *-£107* | *£197* |
| *Zoledronic acid as follow-up treatment* | *£837* | *£1,358* | *£3* | *£48* | *£834* | *£692* | *£977* |
| ***Concomitant medications and treatments*** | | | | | | | |
| *Radiotherapy* | *£764* | *£1,093* | *£1,021* | *£1,264* | *-£257* | *-£429* | *-£85* |
| *Abiraterone* | *£1,811* | *£4,198* | *£2,150* | *£4,478* | *-£339* | *-£993* | *£316* |
| *Zoledronic acid as concomitant medication* | *£235* | *£801* | *£101* | *£492* | *£134* | *£36* | *£230* |
| *Strontium-89 as concomitant medication* | *£98* | *£476* | *£132* | *£539* | *-£34* | *-£109* | *£41* |
| *Blood units* | *£23* | *£150* | *£19* | *£125* | *£4* | *-£16* | *£24* |
| *Cabazitaxel* | *£301* | *£1,710* | *£293* | *£2,230* | *£8* | *-£288* | *£304* |
| *Docetaxel as concomitant medication* | *£372* | *£1,543* | *£433* | *£2,049* | *-£61* | *-£338* | *£216* |
| *Mitoxantrone* | *£51* | *£245* | *£26* | *£179* | *£25* | *-£6* | *£56* |
| *Surgery* | *£116* | *£988* | *£377* | *£1,974* | *-£261* | *-£495* | *-£27* |
| ***Outpatient appointments and inpatient stay*** | | | | | | | |
| *Hospital outpatient appointment* | *£672* | *£1,015* | *£591* | *£804* | *£81* | *-£51* | *£213* |
| *Hospital inpatient stay* | *£3,494* | *£6,216* | *£3,786* | *£6,562* | *-£292* | *-£1,217* | *£632* |
| *GP appointments* | *£278* | *£319* | *£319* | *£384* | *-£42* | *-£95* | *£12* |
| ***TOTAL COST*** | ***£12,667*** | ***£8,795*** | ***£12,417*** | ***£9,433*** | ***£251*** | ***-£1,099*** | ***£1,602*** |
| ***TOTAL QALYs*** | *0.908* | *0.683* | *0.876* | *0.693* | *0.031* | *-0.07* | *0.133* |
| ***** *Obtained using the bias corrected and accelerated bootstrap method (1000 replications)* | | | | | | | |

**Table 3. Mean per-patient cost and QALYS for Sr89 vs no Sr89**

| | Sr89 (n=350) | | No Sr89 (n=357) | | Difference (Sr89 vs no Sr89) | | |
|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | ***Mean difference*** | ***Lower 95% CI**** | ***Upper 95% CI**** |
| ***Trial treatment*** | | | | | | | |
| *Docetaxel + prednisolone* | £2,497 | £738 | £2,445 | £771 | £52 | -£61 | £165 |
| *Zoledronic acid* | £174 | £203 | £168 | £203 | £6 | -£23 | £35 |
| *Strontium 89* | £1,507 | £988 | £0 | £0 | £1,507 | £1,407 | £1,608 |
| *Zoledronic acid as follow-up treatment* | £391 | £965 | £440 | £1,114 | -£49 | -£197 | £100 |
| ***Concomitant medications and treatments*** | | | | | | | |
| *Radiotherapy* | £803 | £1,033 | £983 | £1,318 | -£180 | -£349 | -£11 |
| *Abiraterone* | £1,905 | £4,279 | £2,058 | £4,408 | -£153 | -£814 | £508 |
| *Zoledronic acid as concomitant medication* | £148 | £625 | £187 | £704 | -£39 | -£139 | £61 |
| *Strontium-89 as concomitant medication* | £110 | £527 | £120 | £492 | -£9 | -£85 | £66 |
| *Blood units* | £21 | £150 | £21 | £124 | £0 | -£20 | £21 |
| *Cabazitaxel* | £375 | £2,192 | £221 | £1,765 | £154 | -£134 | £443 |
| *Docetaxel as concomitant medication* | £415 | £2,057 | £390 | £1,545 | £25 | -£233 | £283 |
| *Mitoxantrone* | £39 | £218 | £39 | £211 | £0 | -£32 | £31 |
| *Surgery* | £325 | £1,954 | £172 | £1,064 | £153 | -£84 | £390 |
| ***Outpatient appointments and inpatient stay*** | | | | | | | |
| *Hospital outpatient appointment* | £609 | £889 | £653 | £940 | -£44 | -£178 | £89 |
| *Hospital inpatient stay* | £3,630 | £6,294 | £3,653 | £6,491 | -£23 | -£950 | £903 |
| *GP appointments* | £281 | £350 | £316 | £357 | -£35 | -£86 | £16 |
| ***TOTAL COST*** | **£13,230** | **£9,105** | **£11,865** | **£9,091** | **£1,365** | **-£12** | **£2,742** |
| ***TOTAL QALYs*** | **0.933** | **0.725** | **0.852** | **0.648** | **0.081** | **-0.019** | **0.181** |
| * Obtained using the bias corrected and accelerated bootstrap method (1000 replications) | | | | | | | |

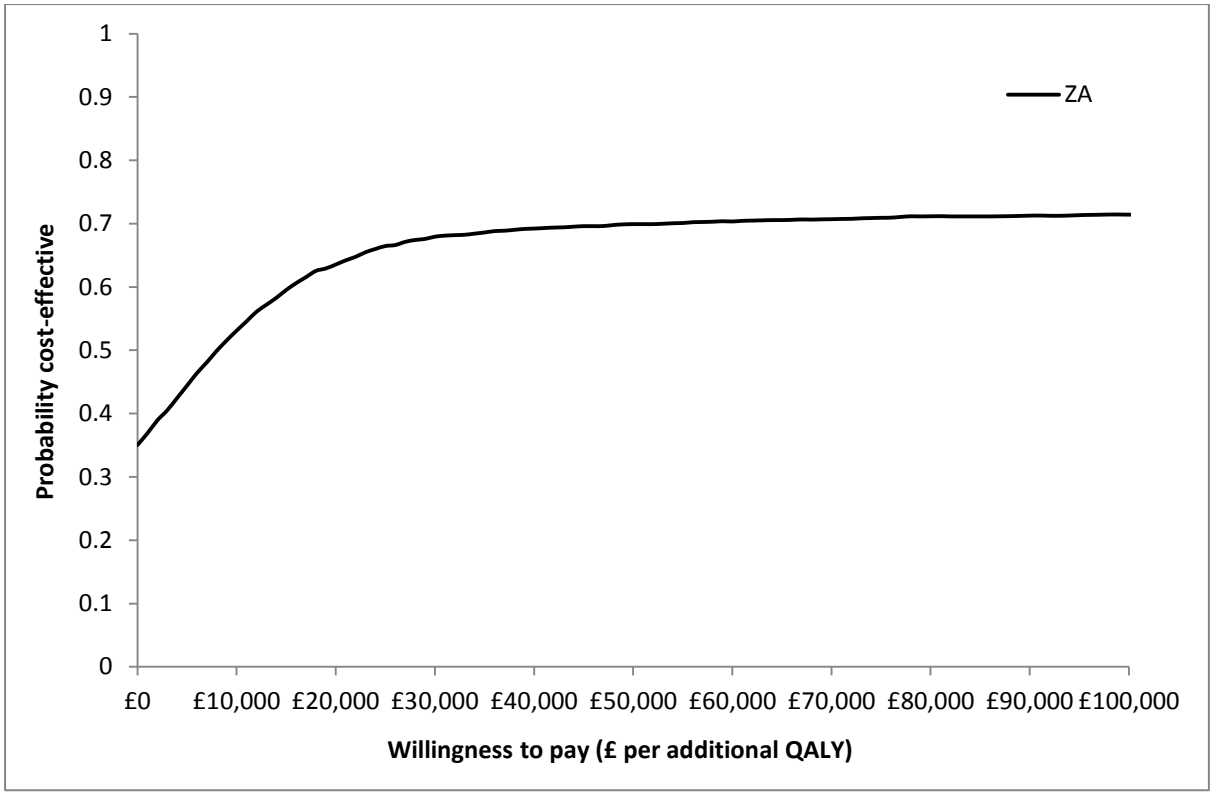


**Figure 1. Cost Effectiveness Acceptability Curve showing the probability of ZA being cost-effective at different values of willingness to pay per additional QALY**

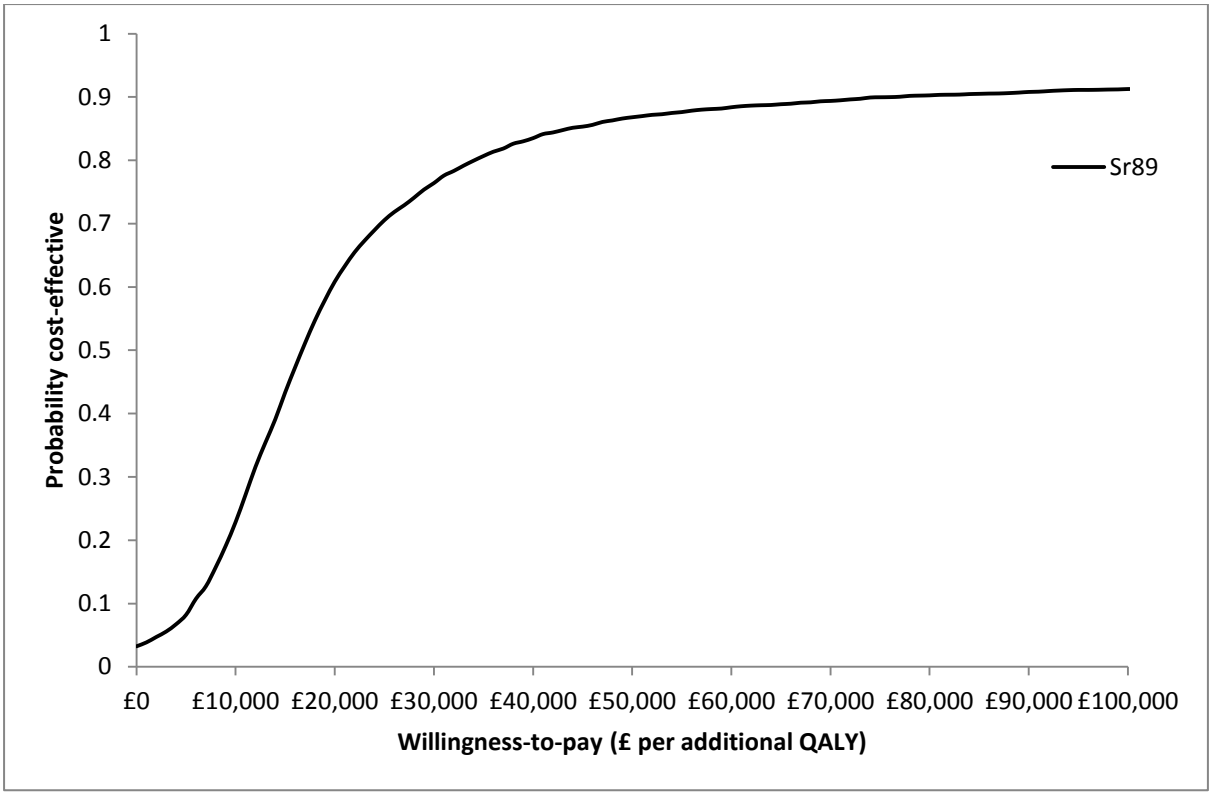


**Figure 2. Cost Effectiveness Acceptability Curve showing the probability of Sr89 being cost-effective at different values of willingness to pay per additional QALY.**

# Supplementary material

**Table S1. Summary characteristics of participants included in the economic evaluation (n=707) and all study participants (n=757)**

| | Economic analysis subset (n=707) | All TRAPEZE trial participants (n=757) |
|---|---|---|
| Age median (IQR) | 68 (64, 73) | 68 (63, 73) |
| PSA median (IQR) | 143.75 (49.8, 347.6) | 145.55 (51.2, 353.58) |
| ECOG n(%) 0 | 291 (41.16) | 305 (40.29) |
| 1 | 361 (51.06) | 389 (51.39) |
| 2 | 55 (7.78) | 63 (8.32) |
| Prior Radiotherapy n (%) | 331 (44.30%) | 337 (44.87%) |
| Daily Present Pain Index (scale 0.5) median (IQR) | 1.43 (0.86, 2.00) | 1.43 (0.86, 2.00) |
| Daily Analgesic Score median (IQR) | 10.01 (0.86, 27.63) | 10.21 (0.88, 27.89) |

**Table S2. Results of sensitivity analyses for ZA vs no ZA and Sr89 vs no Sr89.**

| | ZA | | no ZA | | ICER ZA vs no ZA | Sr89 | | no Sr89 | | ICER Sr89 vs no Sr89 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean Cost | Mean QALYs | Mean Cost | Mean QALYs | | Mean Cost | Mean QALYs | Mean Cost | Mean QALYs | |
| **Base case results** | £12,668 | 0.908 | £12,417 | 0.876 | **£8,005** | £13,230 | 0.933 | £11,865 | 0.852 | **£16,884** |
| **No discounting** | £12,788 | 0.915 | £12,552 | 0.884 | **£7,684** | £13,362 | 0.941 | £11,988 | 0.859 | **£16,806** |
| **Unit cost of mitoxantrone from NHS electronic Market Information Tool (£60.36 for 25mg)** | £12,662 | 0.908 | £12,414 | 0.876 | **£7,914** | £13,226 | 0.933 | £11,861 | 0.852 | **£16,884** |
| **Unit cost of docetaxel taken from NHS electronic Market Information Tool (£34.29 for 140mg)** | £11,515 | 0.908 | £11,227 | 0.876 | **£9,196** | £12,041 | 0.933 | £10,712 | 0.852 | **£16,448** |
| **Unit cost of strontium-89 (75% of base case estimate)** | £12,515 | 0.908 | £12,273 | 0.876 | **£7,718** | £12,931 | 0.933 | £11,865 | 0.852 | **£13,182** |
| **Unit cost of strontium-89 (125% of base case estimate)** | £12,821 | 0.908 | £12,561 | 0.876 | **£8,291** | £13,530 | 0.933 | £11,865 | 0.852 | **£20,585** |

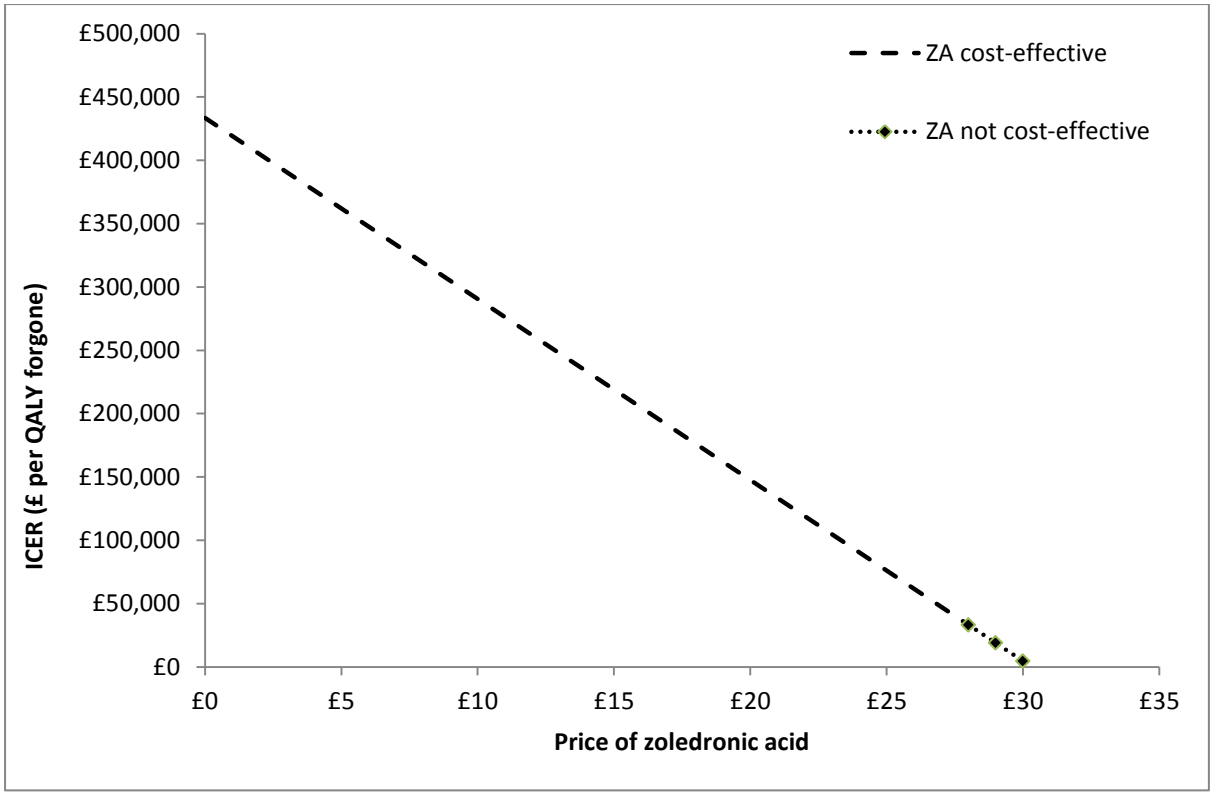


**Figure S1. Graph showing Incremental Cost Effectiveness Ratio for ZA vs no ZA at different prices of zoledronic acid, after adjusting for baseline imbalances in EQ-5D-3L**