# THE COST-EFFECTIVENESS OF THERAPY WITH TERIPARATIDE AND ALENDRONATE IN WOMEN WITH SEVERE OSTEOPOROSIS

## TECHNICAL APPENDIX

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## APPENDIX

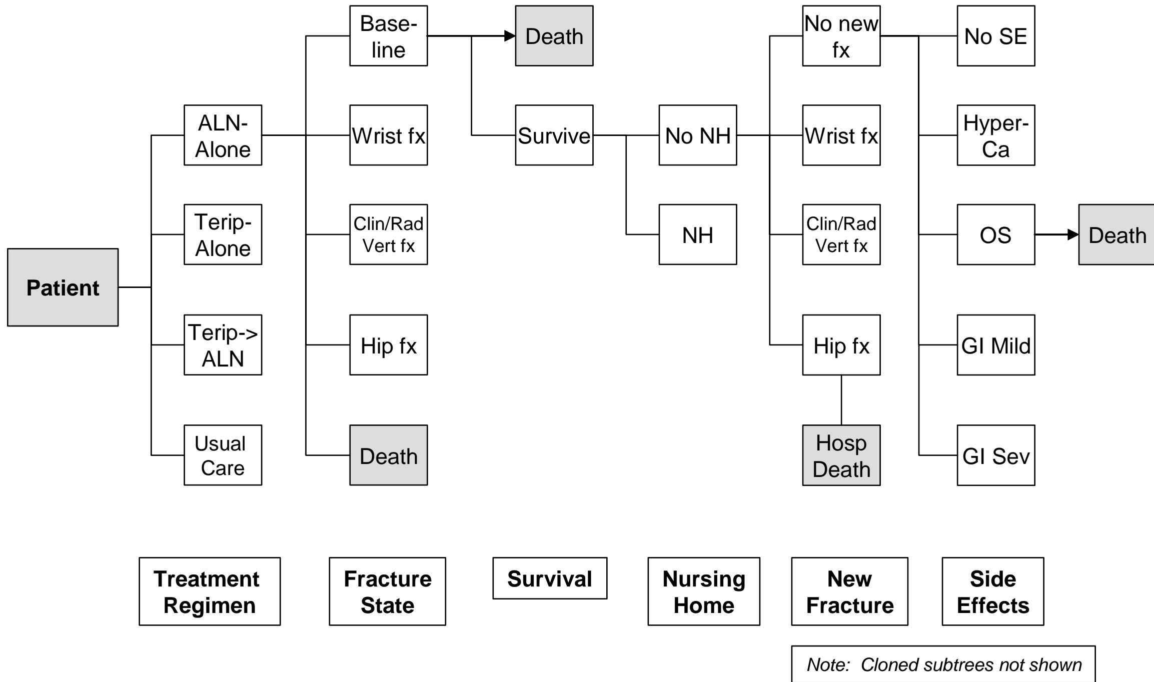
*1. Overview of Model*

Our model is a microsimulation, also referred to as a semi-Markov model. We chose this model structure because it allows the retention of past medical history for each patient that proceeds through the model.[1,2] Individual patients are assigned a cost and utility value for each event and transition that occurs in the model and their final cost and utility is assessed when they complete the model. A high-level schematic of our model is found in Appendix Figure 1. Given that osteoporosis is typically a slowly-progressing illness, we assumed a cycle length of three months.

Each cycle consisted of six key elements. An individual patient is assigned a treatment strategy (usual care, alendronate-alone, teriparatide-alone, or sequential teriparatide/alendronate) and remains in this treatment strategy for the remainder of the model. Within each cycle, the patient is assigned a fracture state based on prior fracture history and severity. The hierarchy of fracture states by inverse severity includes baseline, clinical wrist, morphometric vertebral, clinical vertebral, clinical hip, and death. The baseline state assumes pre-existing vertebral fracture. The patient then may or may not die or enter a nursing home during the cycle based on predetermined mortality and morbidity rates. In addition, the patient can sustain a new fracture or experience an adverse event associated with medication usage. These occurrences are monitored with tracker variables and recorded at the completion of the cycle. At completion of the cycle, the patient either re-starts the cycle, or if deceased, moves to the death fracture state and the model terminates.

Guided by the principles of model-building outlined by Weinstein, et al.,[3] we attempted to validate our model through internal, between-model, and external/predictive validity. Specifically, we performed internal testing of null and extreme values; additionally, we found that our model's baseline fracture rates calibrate well against existing data sources.[4, 5] Our model results for alendronate-alone and teriparatide-alone compared to usual care are comparable to results from other cost-effectiveness analyses.[2, 6-9] Finally, our model structure is highly flexible as new data emerges our model can be adapted to accommodate these findings.

**Appendix Figure 1. Overview of Model**




Abbreviations: alendronate (ALN); teriparatide (Terip); sequential teriparatide/alendronate (Terip->ALN); clinical (Clin); radiologic (Rad); vertebral (Vert); fracture (Fx); nursing home (NH); side effect (SE); hypercalcemia (HyperCa); osteosarcoma (OS); esophagitis (GI Mild); esophageal ulcer (GI Sev); hospital (Hosp)

*2. Usual Care Fracture Rates*

Usual care fracture rates for our model are based on data from the Study of Osteoporotic Fractures (SOF),[10] an observational study of post-menopausal women from the United States designed to evaluate osteoporotic fracture. Data from SOF has been used by the National Osteoporosis Foundation for their comparative analysis of osteoporosis treatments.[11] While SOF enrolled women aged 65 and over, predictions for fracture based on SOF data have been recently validated in younger women,[12] and in a cohort of postmenopausal women from Rochester, MN.[12]

Using the SOF dataset and with the aid of Dennis Black, PhD and Lisa Palermo, MA from the University of California, San Francisco, we constructed logistic regressions to predict future hip, vertebral, and wrist fracture probabilities based on age, femoral neck BMD T-score, and presence or absence of prior vertebral fracture. To mirror today's clinical situation, our baseline cohort from SOF excluded women on any type of estrogen therapy. The regression coefficients are presented in Appendix Table 2. The hip and wrist regression coefficients predict 5-year fracture probabilities. The morphometric vertebral regression coefficients predict 3.7-year fracture probabilities. We assumed that clinical vertebral fractures accounted for 35% of total morphometric fractures[13] and varied this assumption in sensitivity analysis. The 5-year and 3.7-year fracture probabilities were converted to one year rates based on the following equation:

$$\text{Rate} = -\text{LN}\,(1 - \text{Probability}) / \text{Time}$$

where Rate is the one year fracture rate, LN is the natural logarithm, Probability is the 5- or 3.7-year probability of fracture, and Time is the time period in years over which probability

of fracture was determined i.e., 5 or 3.7 years). We used one year fracture rates as inputs for our model.

The effect of calcium and vitamin D supplementation on fracture reduction remains controversial,[14-17] particularly in community-dwelling ambulatory women. As such, in our base case, we assumed that vitamin D and calcium supplementation did not affect SOF-predicted fracture rates (i.e., relative risk = 1). In sensitivity analysis, we decreased this relative risk to 0.7, a level comparable to the fracture relative risk Chapuy and colleagues [16] found with calcium and vitamin D supplementation in a largely vitamin D insufficient population.

**Appendix Table 2. Logistic Regression Coefficients for Usual Care Fracture Prediction**

| Fracture Type | Total N | Constant [SE] | Femoral Neck BMD [SE] (T-Score) | Age [SE] (years) | Prevalent Vertebral Fracture [SE] (1=yes/0=no) |
|---|---|---|---|---|---|
| Clinical Hip Fracture, 5-year probability | 6415 | -10.5957 [0.8815] | -0.9071 [0.0950] | 0.0675 [0.0118] | 0.5072 [0.1504] |
| Clinical Wrist Fracture, 5-year probability | 6397 | -4.1911 [0.9011] | -0.3504 [0.0773] | 0.00392 [0.0125] | -0.0498 [0.1635] |
| Morphometric Vertebral Fracture, 3.7-year probability | 5538 | -7.5023 [0.7775] | -0.4722 [0.0752] | 0.0445 [0.0110] | 1.3781 [0.1248] |

SE = standard error

*3. Baseline and Post-Fracture Mortality Rates*

We used standardized mortality rates (SMR) published by the U.S. National Center for Health Statistics [18] stratified by age and gender for our baseline mortality rates (Appendix Table 3). SOF and other studies have shown excess mortality after hip as well as vertebral fractures,[19-24] although in certain instances, the cause of death may not be closely related to the fracture.[24] Given that our patient population had baseline vertebral fractures, we multiplied the SMR by 1.16 [23] to establish the baseline mortality rate (adjusted-SMR) for this higher-risk population. We assumed that all patients who suffered a hip fracture were hospitalized; the rates of death while hospitalized are shown in Appendix Table 3. In our base case, within the first year of hip fracture, we assumed a substantially increased mortality rate, using published data from the U.S. Office of Technology Assessment's report on hip fractures in the elderly [25] (Appendix 3). After the first year of hip fracture, we assumed continued increased mortality rates, and we multiplied the adjusted-SMR by 2.4 for the remainder of patient's life.[24] We did not assume increased mortality after wrist fracture or for multiple vertebral fractures as compared to the initial vertebral fracture.

**Appendix Table 3. Mortality Rates**

| Area | | Variable |
|---|---|---|
| SMR for U.S. women, selected ages [26] | 50 years old | 0.00326 |
| | 60 years old | 0.00847 |
| | 70 years old | 0.02013 |
| | 80 years old | 0.05105 |
| | 90 years old | 0.15206 |
| SMR multiplier | Post-vertebral fracture | 1.16 [23] |
| | Post-hip fracture (> 1 year after fracture) | 2.4 [24] |
| Hip fracture mortality rate,[25] during Hospitalization | 50-59 years old | 0.01 |
| | 60-69 years old | 0.01 |
| | 70-79 years old | 0.02 |
| | 80-89 years old | 0.03 |
| | 90-99 years old | 0.03 |
| Hip fracture mortality rate [25] after hospitalization, within 1 year of fracture | 50-64 years old | 0.073 |
| | 65-74 years old | 0.105 |
| | 75-84 years old | 0.186 |
| | 85+ years old | 0.329 |

SMR = standardized mortality rate

Note: Probabilities are converted to annual rates as noted in Appendix 2

*4. Costs*

Appendix Table 4a highlights our cost assumptions. We used costs obtained from the Red Book,[27] Center for Medicare and Medicaid Services,[28] and published data on osteoporosis-related costs.[13, 29] We present our findings in 2003 U.S. dollars. When costs were not reported in 2003 dollars, we adjusted them to 2003 levels using the U.S. Consumer Price Index for Medical Care for All Urban Consumers.[30] For our base case fracture costs, we used data presented by Gabriel, et al.[29] We used average costs by fracture type, determined by dividing total fracture-specific cost by the number of patients evaluated with each fracture type. We also evaluated median costs[29] in sensitivity analysis. Annual medical expenditures of postmenopausal Caucasian women, calculated from an analysis of the 2002 U.S. Medical Expenditure Panel Survey (Appendix Table 4b),[31] were not included in our base case analysis but were included in sensitivity analysis. Indirect medical expenditures were also included in sensitivity analysis and were obtained from a recent cost-effectiveness analysis of alendronate.[13] We assumed that clinical vertebral fractures incurred costs, but morphometric vertebral fractures did not. We could not find the cost of an event of osteosarcoma in adults in the medical literature, and thus used a surrogate median cost value from a study evaluating the cost of a range of cancers.[32] We assumed that an episode of esophagitis would require one additional visit to a physician and that an episode of esophageal ulceration would require a hospitalization under DRG code 183 (digestive disorder hospitalization without complications) and two physician visits. We assumed that both of these conditions would also incur costs for proton pump inhibitor therapy for one year.[33] We assumed an episode of hypercalcemia would incur the cost of two physician visits and three calcium blood tests.

**Appendix Table 4a. Costs**

| Area | | Cost ($) |
|---|---|---|
| Annual cost of alendronate [27] | | 894 |
| Annual cost of teriparatide [27] | | 6,720 |
| Direct Medical Costs (per event unless otherwise indicated) | Hip fracture, mean [29] | 17,353 |
| | Clinical vertebral fracture, mean [29] | 7,097 |
| | Wrist fracture, mean [29] | 3,853 |
| | Hip fracture, median [29] | 15,132 |
| | Clinical vertebral fracture, median [29] | 2,632 |
| | Wrist fracture, median [29] | 2,192 |
| | Nursing home care (per year) [34] | 57,700 |
| | Osteosarcoma [32] * | 65,571 |
| | Esophagitis [28] | 50 |
| | Esophageal ulcer [28] | 2,375 |
| | Hypercalcemia [28] | 130 |
| | Proton pump inhibitor (per year) [27] | 240 |
| | Physician visit [28] | 50 |
| | Bone densitometry exam (DXA) [28] | 130 |
| Annual Indirect Medical Costs, Age 70 | Hip fracture [13] | 589 |
| | Clinical vertebral fracture [13] | 250 |
| | Wrist fracture [13] | 159 |

* Surrogate cost, see appendix 4 for details.
All costs adjusted to 2003 U.S. dollars

**Appendix Table 4b. Annual Medical Costs**

| Age | Annual Medical Costs ($) |
|---|---|
| 52.0 | 3,673 |
| 56.9 | 5,152 |
| 61.8 | 5,888 |
| 66.9 | 6,081 |
| 72.0 | 7,793 |
| 77.1 | 7,839 |
| 81.8 | 8.070 |
| 85+ | 8,419 |

Point estimates derived from analysis of variable "TOTEXP02" in the Medical Expenditure Panel Survey[31] grouped by 5-year intervals. Analysis includes only Caucasian women over the age of 50. Values between point estimates were calculated through interpolation. Costs adjusted to 2003 dollars.

5. *Health State Utilities*

Appendix Table 5 highlights our health state utility assumptions. Whenever possible, we used utility values derived from time trade off (TTO) or standard gamble preference measuring methods;[35-37] otherwise we used values based on expert opinion [11] or surrogate values.

During each cycle a patient receives an initial utility based on her age and presence of osteoporosis [35] multiplied by the utility multiplier of having a previous vertebral fracture. If the patient has a new fracture, side effect, or nursing home placement, her utility is modified by the associated utility multiplier. For example, a 70-year old patient at the start of the model has a utility of 0.747 (70 year old, osteoporosis, no fracture [35]) x 0.931 (multiplier, vertebral fracture, subsequent years [38]) = 0.695. If she were to develop a hip fracture, her utility would be 0.695 x 0.797 (multiplier, hip fracture, first year [39]) = 0.554 for the first year after hip fracture. Though the model allows for a new fracture to occur every cycle (three months), the utility is affected only by the current fracture state determined by severity (see Appendix Section 1). In the previous example, if the patient were to get a wrist fracture six months after her hip fracture, her utility would still be 0.554 as the hip fracture states trumps the wrist fracture state.

Health states for which we used surrogate values included: osteosarcoma (value for metastatic ovarian cancer[40]), esophagitis (utility multiplier for hiatal hernia[41]), and esophageal ulcer (utility multiplier for non-specific gastrointestinal ulcer[41]). The utility multiplier for esophagitis was obtained by dividing the mean TTO score for individuals with hiatal hernia in the previous year by the mean TTO score for individuals without hiatal hernia in the previous year from a study that reported these utilities.[41] Likewise, the utility

multiplier for esophageal ulcer was obtained by dividing the mean TTO score for individuals with ulcer in the previous year by the mean TTO score for individuals without ulcer in the previous year.[41] As we could not find a health utility value associated with hypercalcemia, we chose a utility multiplier of 0.98 based on authors' consensus.

As the literature is limited in differentiating the utilities for clinical vertebral fractures alone versus morphometric vertebral fractures alone, for our base case, we used the same utility multiplier (0.82) for morphometric and clinical vertebral fractures in the year immediately following fracture.[38] In sensitivity analysis, we used a lower utility multiplier for the first year immediately following a clinical vertebral fracture (0.62), while maintaining the original common utility for morphometric vertebral fractures (0.82).[38]

**Appendix Table 5. Health State Utilities**

| Area | | Utility |
|---|---|---|
| Osteoporosis, no fracture [35] | Ages 65-69 | 0.806 |
| | Ages 70-74 | 0.747 |
| | Ages 75-79 | 0.731 |
| | Ages 80-85 | 0.699 |
| | Ages 85+ | 0.676 |
| Hip fracture * | First year [39] | 0.797 |
| | Subsequent years [35] | 0.900 |
| Vertebral fracture * | First year [38] | 0.820 |
| | Subsequent years [38] | 0.931 |
| Clinical vertebral fracture * § | First year [38] | 0.620 |
| | Subsequent years [38] | 0.931 |
| Wrist fracture * | First year [37] | 0.981 |
| | Subsequent years [35] | 1.000 |
| Osteosarcoma †* [40] | | 0.63 |
| Esophagitis †* [41] | | 0.98 |
| Esophageal ulcer †* [41] | | 0.91 |
| Hypercalcemia *‡ | | 0.98 |
| Nursing home stay * [35] | | 0.40 |

* Utility multiplier values; † Surrogate utility value; ‡ Utility value based on authors' consensus opinion; § utility used in sensitivity analysis

*6. Nursing Home Parameters*

We used the U.S. Office of Technology Assessment's study on hip fractures in the elderly,[25] and other long-term studies [42-44] to determine rates of nursing home admission, length of stay, discharge, and mortality rates for hip fracture patients. Appendix Table 6 highlights these assumptions. Appendix Table 4a highlights the costs associated with nursing home care.

**Appendix Table 6. Nursing Home Parameters**

| Area | | Rate | Percentage (%) | |
|---|---|---|---|---|
| Hip fracture mortality rate [25] after hospitalization within one year of fracture | 50 years old | 0.07257 | | |
| | 65 years old | 0.10536 | | |
| | 75 years old | 0.18632 | | |
| | 85 years old | 0.32850 | | |
| Present to nursing home following hip fracture [43, 45] | | | 60 | |
| Percentage remaining in nursing home after: [44] | Age 55-64 | Age 65-74 | Age 75-84 | Age 85+ |
| 90 days | 65.0 | 63.4 | 70.6 | 76.1 |
| 182 days | 49.9 | 52.4 | 59.9 | 65.6 |
| 365 days (1 year) | 35.4 | 40.7 | 47.5 | 51.9 |
| 730 days (2 years) | 23.9 | 28.9 | 33.4 | 34.7 |
| 1,642 days (4.5 years) | 13.1 | 13.3 | 12.4 | 8.9 |

*7. Adverse Event Assumptions*

We considered the following adverse events: mild hypercalcemia and osteosarcoma (teriparatide), and esophagitis and esophageal ulceration (alendronate). We assumed that patients who experienced osteosarcoma or esophageal ulceration discontinued their teriparatide or alendronate therapy and received treatment, and that their fracture rates returned to usual care levels in a linear fashion over five years.[2, 46-48] Patients experiencing osteosarcoma received a one-time toll for the cost of the event and its associated disutility (see Appendix Tables 4a and 5). For model simplicity, we assumed that all patients who developed osteosarcoma died in three years. As no known cases of osteosarcoma due to teriparatide have occurred in humans, we set the rate of osteosarcoma to 0% in our base case. For patients who experiences esophageal ulceration, we assumed they underwent hospitalization, one year of proton pump inhibitor (PPI) treatment, and two additional outpatient physician visits (Appendix Table 4a). We assumed that patients who experienced esophagitis received PPI treatment for one year, an additional outpatient physician visit, and continued alendronate therapy.[33] We assumed that patients who experienced hypercalcemia received increased monitoring (two additional physician visits and three calcium blood tests) and continued teriparatide therapy. We based adverse event rates on published clinical trial data [5, 49] and varied these assumptions in sensitivity analysis (Table 3). Adverse event assumptions are listed in Appendix Table 7.

**Appendix Table 7. Adverse Event Assumptions**

| Adverse Event | Annual Rate, Base Case |
|---|---|
| Esophagitis, Alendronate [5] | 0.001 |
| Esophageal Ulceration, Alendronate [5] | 0.001 |
| Hypercalcemia, Teriparatide [49] | 0.058 |
| Osteosarcoma, Teriparatide [49] | 0.000 |

Note: These rates were varied in sensitivity analysis; see Table 3 for details.

*8. Fracture Risk Reduction: Base Case and Scenarios*

To determine rates of fracture on therapy, we formulated relative risk curves for each treatment strategy and multiplied these risks by usual care fracture rates. We assumed that fracture risk reduction reached published rates [5, 49] at the start of therapy.[2, 13] In our base case analysis, we assumed that alendronate was used for five years, and teriparatide was used for two years.

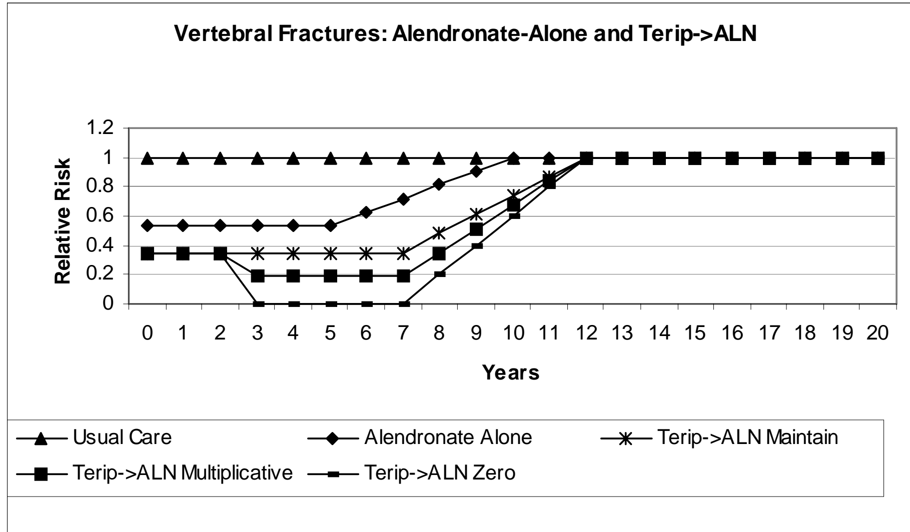
For our base case analysis, we assumed a linear offset time (time that medication maintains anti-fracture effect) of five years for both alendronate and teriparatide therapy after cessation of the single drug treatment strategies (alendronate-alone and teriparatide-alone).[50] To determine the effect of the offset time on the cost-effectiveness of teriparatide-alone, we varied the offset time of teriparatide from one to fifteen years.

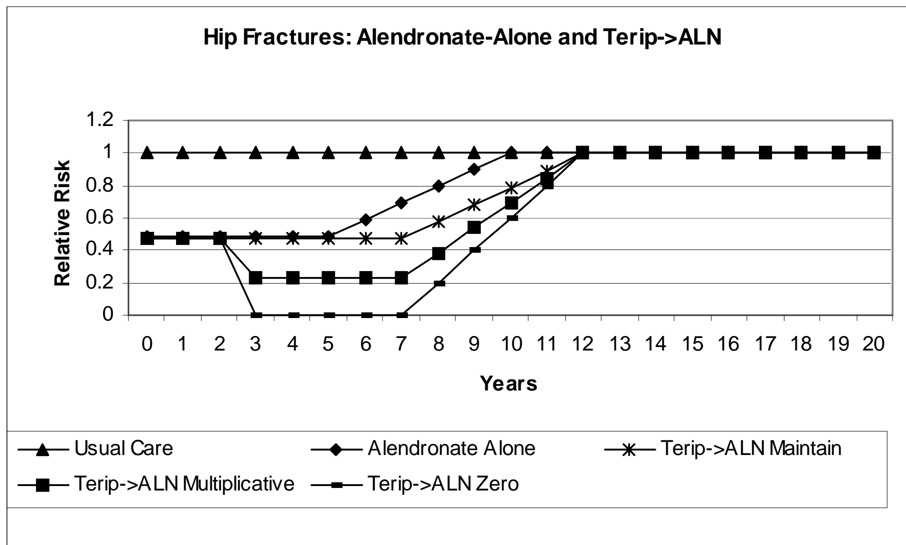
For our base case, we assumed that teriparatide reduced hip fractures at the non-vertebral fracture rate reported in the Teriparatide Fracture Prevention Trial (FPT).[49] This trial was powered to detect specific non-vertebral fracture improvements at 3 years, but was stopped at 19 months due to findings of osteosarcoma in rats treated with teriparatide and could only detect a significant decrease in all non-vertebral fractures (relative risk = 0.47). Although not significant given small numbers, the data from Table 3 of the study suggest that teriparatide at 20 mcg/d may reduce specific non-vertebral fractures (placebo vs PTH 20mcg: hip fractures, 4 vs 2; wrist fractures, 13 vs 7) also by about 50%. We therefore used the non-vertebral fracture rate as a surrogate for hip and wrist fracture rates. In sensitivity analysis, we also evaluated the cost-effectiveness of teriparatide assuming that if it did not decrease hip or wrist fractures (relative risk = 1) or assuming that it decreased hip and wrist fractures 30% better than the non-vertebral fracture rate (relative risk = 0.33) reported in the FPT.

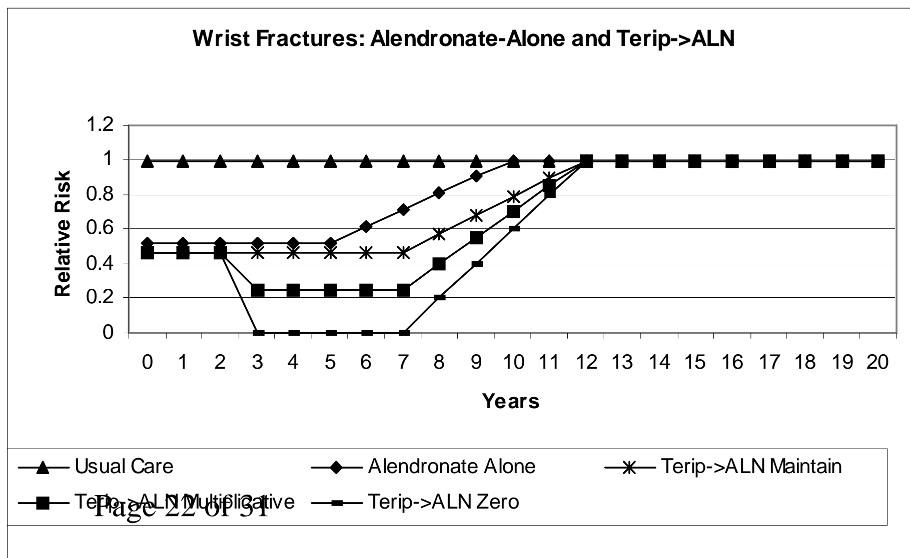
For the base case for sequential teriparatide/alendronate therapy, we assumed that alendronate would reduce fractures after two years of teriparatide therapy in the same proportion as it would in a treatment-naïve patient ("Multiplicative" scenario). For example, we assumed a relative risk of 0.53 for vertebral fracture while on alendronate therapy,[5] and 0.35 when on teriparatide therapy.[49] We therefore assumed subsequent alendronate therapy would result in fracture relative risk of 0.19 (i.e., 0.53 x 0.35) while on alendronate. We also examined two other scenarios, one in which alendronate therapy after teriparatide therapy eliminated vertebral, hip, and wrist fractures ("Zero" scenario), and another in which alendronate only maintained the fracture benefits gained while on teriparatide ("Maintain" scenario). In all scenarios, we assumed a linear offset time of five years upon cessation of alendronate therapy.[50]

The following graphs show the assumptions for fracture relative risk with treatment (alendronate-alone, teriparatide-alone, and sequential teriparatide/alendronate) compared to usual care fracture rates by number of years of treatment. Appendix Figure 8a highlights the fracture relative risk curves for alendronate-alone and sequential teriparatide/alendronate (including the "Multiplicative", "Zero", and "Maintain" scenarios), and Appendix Figure 8b highlights the fracture relative risk curves for teriparatide-alone (with varying offset times from one to fifteen years).

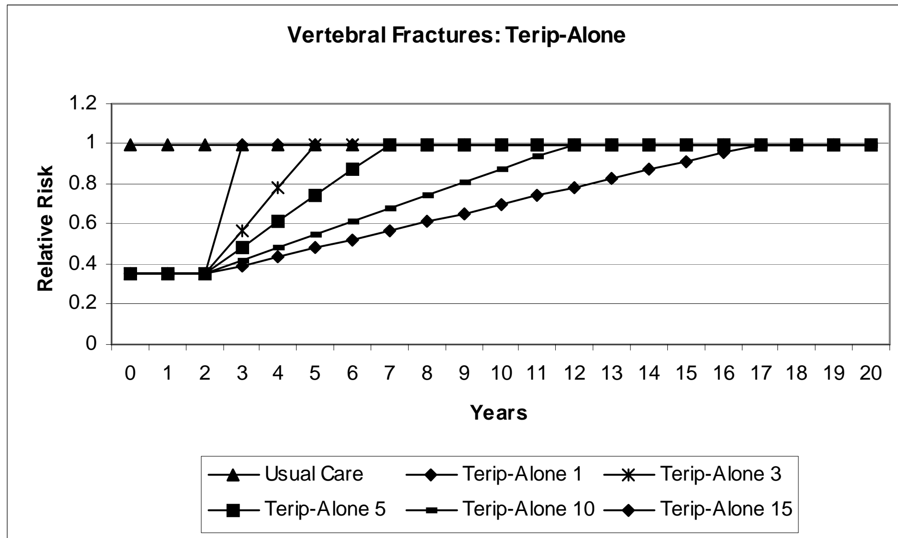
**Appendix Figure 8a. Fracture Risk Reduction Curves for Usual Care, Alendronate-alone, and Sequential Teriparatide/Alendronate (Terip->ALN)**

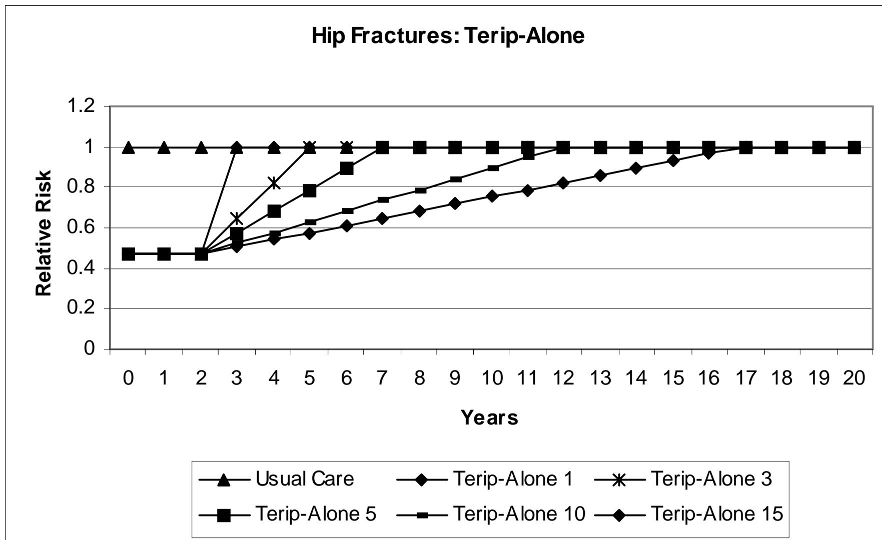


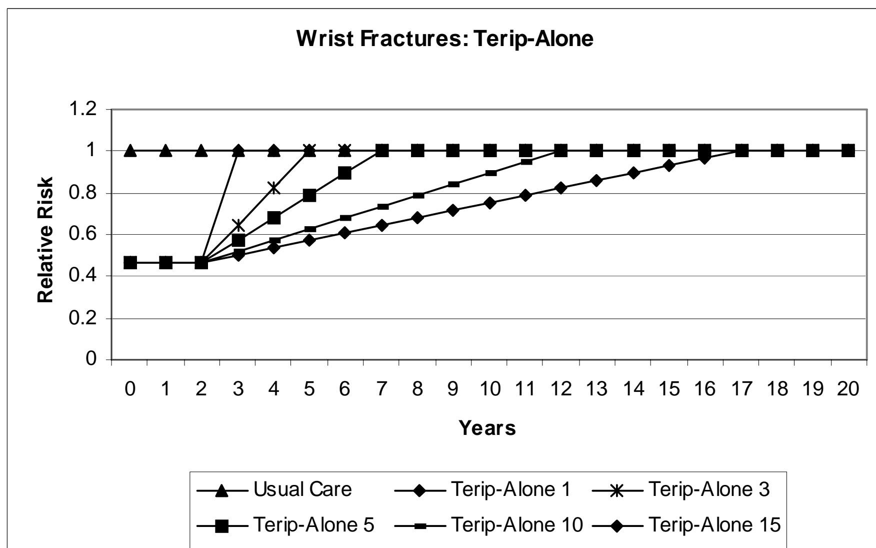



**Appendix Figure 8b. Fracture Risk Reduction Curves for Usual Care and Teriparatide-Alone (Terip-Alone)**



9. *Sensitivity Analyses*

We performed sensitivity analyses on model parameters to assess the robustness of our results. The sensitivity analyses for the offset time of teriparatide and the fracture efficacy of alendronate following teriparatide have been described in the section above. The details and assumptions for other sensitivity analyses are shown in Appendix Table 9.

## Appendix Table 9. Sensitivity Analyses Assumptions

| Parameter | Scenario (if indicated) | Sensitivity Analysis Assumptions |
|---|---|---|
| Teriparatide Annual Price | | • Price variation: 100% ($6720) [27], 75% ($5040), 50% ($3360), 40% ($2688), 25% ($1680) |
| Alendronate Annual Price | | • Price variation: 100% ($894) [27], 75% ($671), 50% ($447), 25% ($224) |
| Femoral Neck BMD T-Score | | • Analyze at T-score of -2.5, -3.0, -3.5, and -4.0<br>• Baseline fracture rates derived from logistic regressions from Appendix 2 |
| Age | | • Analyze at age 50, 60, 70, and 80<br>• Baseline fracture rates derived from logistic regressions from Appendix 2 |
| Teriparatide Treatment Length | | • Vary teriparatide treatment length: 0.5, 1.0, 1.5 and 2.0 (base case) years for teriparatide-alone and sequential teriparatide/alendronate<br>• For each treatment length scenario, assume teriparatide attains base case fracture reduction efficacy during teriparatide treatment<br>• Other fracture assumptions remain unchanged |
| Adverse Events | Alendronate poorly tolerated, Teriparatide well tolerated | • Set adverse events: Alendronate: esophagitis at 30%, esophageal ulceration at 5%; Teriparatide: hypercalcemia at 0%, osteosarcoma at 0% |
| | Teriparatide: osteosarcoma 100x baseline rates | • Baseline rate of osteosarcoma 2 per million per annum [51]<br>• Set osteosarcoma rate in teriparatide-treated patients at 200 per million per annum |
| Clinical Vertebral Fractures | 20% | • Assume 20% of morphometric vertebral fractures are clinical fractures |
| (% of morphometric fractures) | 50% | • Assume 50% of morphometric vertebral fractures are clinical fractures |
| Costs | Include annual medical expenditures | • Annual medical expenditures derived from analysis shown in Appendix 4b |
| | Include indirect medical costs | • Indirect medical costs included in analysis, obtained from reference [13] |
| | Median fracture costs used | • Use median (rather than mean) fracture costs [29] |
| | Fracture costs 30% higher | • Fracture costs (from Appendix 3) multiplied by 1.3 |
| | Fracture costs 30% lower | • Fracture costs (from Appendix 3) multiplied by 0.7 |
| Discount Rate | 5% | • Discount rate set to 5% |
| | 7% | • Discount rate set to 7% |
| Fracture Rates | All fractures 30% higher (RR = 1.3) [+] | • Multiply baseline fracture rates for hip, wrist, and vertebra by 1.3 and set as new usual care fracture rate |
| (change from usual care rates) | All fractures 30% lower (RR = 0.7) [+] | • Multiply baseline fracture rates for hip, wrist, and vertebra by 0.7 and set as new usual care fracture rate |
| | Vertebral fractures 30% higher | • Multiply baseline fracture rates for vertebra by 1.3 and set as new usual care fracture rate |
| Health State Utilities | Clinical vertebral fracture utility 0.62 during 1st year after fracture | • Use utility multiplier of 0.62 for clinical vertebral fracture for first year after vertebral fracture (Appendix 5) |

| | | |
|---|---|---|
| | | • Beginning one year after vertebral fracture, use utility multiplier of 0.931 (same as morphometric vertebral fracture) |
| | Age-adjusted health utilities 30% higher | • Multiply baseline osteoporosis health state utilities (without fracture) (Appendix 5) by 1.3<br>• If utility exceeded 1, set to 1 |
| | Age-adjusted health utilities 30% lower | • Multiply baseline osteoporosis health state utilities (without fracture) (Appendix 5) by 0.7 |
| | Fracture health utility multipliers 30% higher | • Multiply hip, wrist, and vertebral fracture utility multipliers, including first year and subsequent years, (Appendix 5) by 1.3<br>• If utility exceeded 1, set to 1 |
| | Fracture health utility multipliers 30% lower | • Multiply hip, wrist, and vertebral fracture utility multipliers, including first year and subsequent years, (Appendix 5) by 0.7 |
| Intervention Compliance | Alendronate 80%, Teriparatide 80% | • Assume compliance with alendronate and teriparatide is 80%<br>• Assume if patient non-compliant, filled prescription for 1 month, but does not/rarely takes medication during month, resulting in no clinical benefit<br>• Calculate average cost and quality-adjusted life year at new compliance rate (not including 1 month drug cost) based on following equation:<br>○ Y = [X * Tt] + [(1-X) * Tuc]<br>▪ Y = cost or quality-adjusted life year<br>▪ X = % compliance<br>▪ Tt = summary data (cost or quality-adjusted life year) for treated group (using value from base case)<br>▪ Tuc = summary data (cost or quality-adjusted life year) for usual care<br>• Add one month's cost of medication to newly calculated average cost, resulting in new average cost for each treatment group<br>• Assume no change to new calculated quality of life value |
| | Alendronate 50%, Teriparatide 50% | • Assume compliance with alendronate and teriparatide 50%<br>• Method same as that for compliance of 80% |
| Mortality | Fourteen percent of post-hip fracture mortality due to hip fracture | • Assume 14% of post-hip fracture mortality directly due to hip fracture[24]<br>• Identify in treated groups subjects who did not fracture hip due to intervention but would have otherwise transitioned to death state<br>• Increase mortality rate in this population to post-hip fracture mortality rates less 14% of this rate |
| Teriparatide Fracture Reduction Efficacy | Vertebral fractures eliminated while on teriparatide therapy | • If on teriparatide therapy, assume future morphometric and clinical vertebral fractures eliminated (relative risk = 0)<br>• For teriparatide-alone, assume 5 year linear offset time for vertebral fractures from relative risk of 0 once teriparatide stopped<br>• For sequential teriparatide/alendronate, assume that vertebral fractures remain eliminated while on alendronate therapy, then 5 year linear offset time for vertebral fractures from relative risk of 0 once alendronate stopped |

| | | |
|---|---|---|
| | Relative risk of hip and wrist fractures for teriparatide increased to 1.0 | • Assume no fracture reduction for non-vertebral fractures (hip, wrist) while on teriparatide (relative risk = 1) |
| | Relative risk of hip and wrist fractures for teriparatide decreased to 0.33 | • Assume anti-fracture benefit of teriparatide 30% better for hip and wrist fractures than base case<br>• Decrease relative risk for teriparatide for hip and wrist fractures from 0.47 to 0.33 |
| | Decreased anti-fracture benefit achieved with sequential therapy | • Assume that anti-fracture efficacy of sequential therapy relative risk not as optimistic as base case<br>• Assume that fracture relative risk for vertebral/hip/wrist fracture is 0.26/0.35/0.35 during the alendronate phase of sequential therapy (base case 0.19/0.26/0.26) |
| Therapy Parameters | Alendronate for 5 years, decrease to usual care fracture rates over 10 years | • Assume treat with 5 years (same as base case)<br>• Linear offset to usual care fracture rates over 10 years |
| | Alendronate for 10 years, decrease to usual care fracture rates over 5 years | • Assume treat with 10 years, assume fracture relative risks on treatment same as 5 year treatment assumptions<br>• Linear offset to usual care fracture rates over 5 years |
| | Alendronate and teriparatide with decrease to usual care fracture rates over 1 year after therapy cessation | • Assume both alendronate and teriparatide with linear decrease to usual care fracture rates one year after therapy cessation |

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