Cost-Effectiveness of Pharmacological Treatments for Osteoporosis Consistent with the Revised Economic Evaluation Guidelines for Canada

Online Appendix: Calibration of Transition Probabilities and Validity of Model
1. Calibration of Transition Probabilities

Background

Often when populating decision models values relating to particular input parameters are unavailable. However, these parameters can be derived from other existing data. For example, the probability of an event within the community as well as the relative risk of the event given a risk factor may be available. Simply weighting the community risk with the relative risk will give an over estimate of the risk in both the population with and without the risk factor. Calibration can allow for the calculation of the appropriate estimate for both parameters.

Calibration within the Current Economic Evaluation

The current study was designed to assess the cost-effectiveness of pharmacological treatment of osteoporosis for post-menopausal women. Stratified analysis was used to determine the optimal treatment based on a woman’s age and fracture history.

The probability of a woman experiencing a hip, wrist or vertebral fracture is assumed to be dependent on three factors; age, osteoporotic status and previous history of osteoporotic fractures. Both hip and vertebral fractures are associated with excess mortality and hip fractures are also associated with increased admission to long term care facilities (LTC). In addition, the probability of hip fracture and the probability of mortality post hip fracture increases if a woman resides within LTC.

Given the structure of the model and the decision problem it addresses, the following transition probabilities are required to allow a simulation of progression for post-menopausal women aged over 65 with osteoporosis through the model:

- Probability of hip, wrist and spine fracture specific to a woman’s age, residential status, osteoporotic history and treatment.
- Probability of being admitted to LTC specific to a woman’s age and whether they have in the past year experienced a hip fracture
- Probability of mortality specific to a woman’s age, whether they live in LTC or the community and whether they have in the past year experienced a hip or vertebral fracture
The full list of necessary transition probabilities which will vary by a woman’s age is therefore

- Probability of hip fracture for those living in the community with osteoporosis and no previous osteoporotic fracture
- Probability of hip fracture for those living in LTC with osteoporosis and no previous osteoporotic fracture
- Probability of hip fracture for those living in the community with previous osteoporotic fracture
- Probability of hip fracture for those living in LTC with previous osteoporotic fracture
- Probability of vertebral fracture for those with osteoporosis and no previous osteoporotic fracture
- Probability of vertebral fracture for those with previous osteoporotic fracture
- Probability of wrist fracture for those with osteoporosis and no previous osteoporotic fracture
- Probability of wrist fracture for those with previous osteoporotic fracture
- Probability of admission to LTC without a hip fracture in the past year
- Probability of admission to LTC following a hip fracture in the past year
- Probability of death without hip or vertebral fracture in the past year for those living in the community
- Probability of death without hip or vertebral fracture in the past year for those living in LTC
- Probability of death following a hip fracture in the past year for those living in the community
- Probability of death following a vertebral fracture in the past year for those living in the community
- Probability of death following a hip fracture in the past year for those living in LTC
- Probability of death following a vertebral fracture in the past year for those living in LTC

In many instances, the required data are unavailable. However, alternative data parameters are available which allow computation of the necessary parameters which would replicate the available data through calibration of the model. To determine these values the calibration exercise required creating a revised model which allowed the simulation of the total population of 50 year old women thus incorporating the incidence of osteoporosis. The purpose was to ensure that the transition probabilities employed in the economic model replicated all available data especially those at a population level ensuring convergent validity.
Thus, for the calibration an alternative model schematic was adopted which included a state related to women without osteoporosis (Figure 1).

**Figure 1 Model Schematics**

![Model Schematics](image)

a. Schematic used in economic evaluation
b. Schematic required for model calibration

The calibration process required the following additional transition probabilities to be estimated:

- Probability of developing osteoporosis without an incident osteoporotic fracture by a woman’s age
- Probability of hip fracture for non-osteoporotic women living in the community
- Probability of hip fracture for non-osteoporotic women living in LTC
- Probability of vertebral fracture for non-osteoporotic women
- Probability of wrist fracture for non-osteoporotic women

The need for calibration and how the process worked for both mortality and for hip fracture are provided in detail.

**Calibration of mortality data**

For the conduct of the economic evaluation it is necessary to obtain age specific probability of death for women who experience fracture and those who do not and to allow for the increased risk of death associated with living in LTC. The six age-specific probabilities relating to death that are required within the model are:

- Probability of death without hip or vertebral fracture in the past year for those living in the community — \( p_{\text{death}|\text{no fracture}|\text{community}} \)
- Probability of death without hip or vertebral fracture in the past year for those living in LTC — \( p_{\text{death}|\text{no fracture}|\text{LTC}} \)
- Probability of death following a hip fracture in the past year for those living in the community — \( p_{\text{death}|\text{hip fracture}|\text{community}} \)
- Probability of death following a vertebral fracture in the past year for those living in the community — \( p_{\text{death}|\text{vertebral fracture}|\text{community}} \)
- Probability of death following a hip fracture in the past year for those living in LTC— \( p_{\text{death}|\text{hip fracture}|\text{LTC}} \)
- Probability of death following a vertebral fracture in the past year for those living in LTC— \( p_{\text{death}|\text{vertebral fracture}|\text{LTC}} \)

The age-specific probability of death for all-causes was available — \( p_{\text{death}|\text{all cause}} \).
The model can predict the proportion of the total population at any age which either

- Live in the community (prop\textsubscript{community})
- Live in the community and experience a hip fracture - (prop\textsubscript{hip fracture}|community)
- Live in LTC and experience a hip fracture – (prop\textsubscript{hip fracture}|LTC)
- Live in the community and experience a vertebral fracture - (prop\textsubscript{vertebral fracture}|community)
- Live in LTC and experience a vertebral fracture – (prop\textsubscript{vertebral fracture}|LTC)

By definition (equation 1):

\[
\begin{align*}
& p \text{death|no fracture|community} \times (\text{prop\textsubscript{community}-prop\textsubscript{hip fracture|community}}) + \\
& (p \text{death|hip fracture|community}) \times \text{prop\textsubscript{hip fracture|community}} + \\
& (p \text{death|vertebral fracture|community}) \times \text{prop\textsubscript{vertebral fracture|community}} + \\
& p \text{death|no fracture|LTC} \times (1 - \text{prop\textsubscript{community}-prop\textsubscript{hip fracture|LTC}-prop\textsubscript{vertebral fracture|LTC}) + \\
& (p \text{death|hip fracture|LTC}) \times \text{prop\textsubscript{hip fracture|LTC}} + \\
& (p \text{death|vertebral fracture|LTC}) \times \text{prop\textsubscript{vertebral fracture|LTC}} = \\
& p \text{death|all cause}
\end{align*}
\]

The relative risk of mortality associated with vertebral fracture (rr\textsubscript{death|vertebral fracture}), hip fracture (rr\textsubscript{death|hip fracture}) and living in LTC (rr\textsubscript{death|LTC}) are known.

Thus, by definition (equations 2-6):

\[
\begin{align*}
& p \text{death|hip fracture|community} = p \text{death|no fracture|community} \times \text{rr\textsubscript{death|hip fracture}} \\
& p \text{death|vertebral fracture|community} = p \text{death|no fracture|community} \times \text{rr\textsubscript{death|vertebral fracture}} \\
& p \text{death|no fracture|LTC} = p \text{death|no fracture|community} \times \text{rr\textsubscript{death|LTC}} \\
& p \text{death|hip fracture|LTC} = p \text{death|no fracture|community} \times \text{rr\textsubscript{death|hip fracture}} \times \text{rr\textsubscript{death|LTC}} \\
& p \text{death|vertebral fracture|LTC} = p \text{death|no fracture|community} \times \text{rr\textsubscript{death|vertebral fracture}} \times \text{rr\textsubscript{death|LTC}}
\end{align*}
\]
Thus, by substituting the above set of equations (equation 2-6) into the original equation (equation 1) we obtain (Equation 7).

\[
\Pr(\text{death} | \text{no fracture} | \text{community}) = \Pr(\text{death} | \text{all cause}) / \left[ \left( \Pr(\text{community}) - \Pr(\text{hip fracture} | \text{community}) - \Pr(\text{vertebral fracture} | \text{community}) \right) + \Pr(\text{death} | \text{vertebral fracture}) \Pr(\text{hip fracture} | \text{community}) + \Pr(\text{death} | \text{vertebral fracture}) \Pr(\text{vertebral fracture} | \text{community}) + \Pr(\text{death} | \text{LTC}) \left( 1 - \Pr(\text{community}) - \Pr(\text{hip fracture} | \text{LTC}) - \Pr(\text{vertebral fracture} | \text{LTC}) \right) + \Pr(\text{death} | \text{hip fracture}) \Pr(\text{LTC}) \Pr(\text{hip fracture} | \text{LTC}) + \Pr(\text{death} | \text{LTC}) \Pr(\text{vertebral fracture} | \text{LTC}) \right] 
\]

From this, we can then obtain the probability of death for all other states based on equations 2 to 6.
Calibration of hip fracture data

The calibration of hip fracture data was much more complex. For the conduct of the economic evaluation, four specific age-specific probabilities for hip fracture were required:

- Probability of hip fracture for those living in the community with osteoporosis and no previous osteoporotic fracture – \( p_{\text{hip fracture}|\text{osteo}|\text{no previous}|\text{community}} \)
- Probability of hip fracture for those living in LTC with osteoporosis and no previous osteoporotic fracture – \( p_{\text{hip fracture}|\text{osteo}|\text{no previous}|\text{LTC}} \)
- Probability of hip fracture for those living in the community with prior osteoporotic fracture – \( p_{\text{hip fracture}|\text{previous}|\text{community}} \)
- Probability of hip fracture for those living in LTC with prior osteoporotic fracture – \( p_{\text{hip fracture}|\text{previous}|\text{LTC}} \)

To allow for the calibration exercise – two further probabilities were required:

- Probability of hip fracture for non-osteoporotic women living in the community – \( p_{\text{hip fracture}|\text{no osteo}|\text{community}} \)
- Probability of hip fracture for non-osteoporotic women living in LTC – \( p_{\text{hip fracture}|\text{no osteo}|\text{LTC}} \)

The age specific probability of hip fracture for all women was available - \( p_{\text{hip fracture}|\text{all}} \).

The model can predict the proportion of the total population at any age which either

- Live in the community (\( \text{prop}_{\text{community}} \))
- Live in the community with osteoporosis (\( \text{prop}_{\text{osteo}|\text{community}} \))
- Live in the community with prior fracture (\( \text{prop}_{\text{prior}|\text{community}} \))
- Live in long term case with osteoporosis (\( \text{prop}_{\text{osteo}|\text{LTC}} \))
- Live in LTC with prior fracture (\( \text{prop}_{\text{prior}|\text{LTC}} \))
By definition (equation 9):

\[
\begin{align*}
P_{\text{hip fracture|no osteo|community}} & \cdot (\text{prop}_{\text{community}} - \text{prop}_{\text{osteop|community}}) + \\
P_{\text{hip fracture|osteop|no previous|community}} & \cdot (\text{prop}_{\text{osteop|community}} - \text{prop}_{\text{previous|community}}) + \\
P_{\text{hip fracture|previous|community}} & \cdot \text{prop}_{\text{previous|community}} + \\
P_{\text{hip fracture|no osteop|LTC}} & \cdot (1 - \text{prop}_{\text{community}} - \text{prop}_{\text{osteop|LTC}}) + \\
P_{\text{hip fracture|osteop|no previous|LTC}} & \cdot (\text{prop}_{\text{osteop|LTC}} - \text{prop}_{\text{previous|LTC}}) + \\
P_{\text{hip fracture|previous|LTC}} & \cdot \text{prop}_{\text{previous|LTC}} = \\
P_{\text{hip fracture|all}}
\end{align*}
\]

The relative risk of hip fracture associated with a previous fracture for an osteoporotic woman (\(rr_{\text{hip fracture|osteop|previous}}\)) and the relative risk of a hip fracture if living in LTC (\(rr_{\text{hip fracture|LTC}}\)) are known.

The relative risk of a hip fracture for an individual’s bone mineral density being one standard deviation lower based on the bone mass of a young adult is known. For each age group, data were available on the average bone mass of women and their dispersion. From this, it was possible to estimate the average bone mass for a women with osteoporosis and an average women without osteoporosis. Based on this, for each age group the relative risk for a hip fracture for osteoporotic versus non-osteoporotic women was estimated (\(rr_{\text{hip fracture|osteop}}\)). From this the relative risk of a hip fracture for an osteoporotic women with no previous fracture is estimated as follows (\(rr_{\text{hip fracture|osteop|no previous}}\)).
By definition (equation 10)

$$rr_{\text{hip fracture|osteo}} = (\text{prop}_{\text{osteo|community}} - \text{prop}_{\text{previous|community}}) * rr_{\text{hip fracture|osteo|no previous}} + \text{prop}_{\text{previous|community}} * rr_{\text{hip fracture|osteo|previous}} + \text{prop}_{\text{osteo|LTC}} - \text{prop}_{\text{previous|LTC}}) * rr_{\text{hip fracture|LTC}} * rr_{\text{hip fracture|osteo|previous}} + \text{prop}_{\text{previous|LTC}} * rr_{\text{hip fracture|LTC}} * rr_{\text{hip fracture|osteo|no previous}}$$

We can arrange this formula to solve for the only unknown factor (equation 11)

$$rr_{\text{hip fracture|osteo|no previous}} = \frac{rr_{\text{hip fracture|osteo}}} {[ (\text{prop}_{\text{osteo|community}} - \text{prop}_{\text{previous|community}}) + \text{prop}_{\text{previous|community}} * rr_{\text{hip fracture|osteo|previous}} + (\text{prop}_{\text{osteo|LTC}} - \text{prop}_{\text{previous|LTC}}) * rr_{\text{hip fracture|LTC}} + \text{prop}_{\text{previous|LTC}} * rr_{\text{hip fracture|LTC}}]}$$

Thus, we can provide the following formulae (equations 12-16)

$$P_{\text{hip fracture|osteo|no previous|community}} = P_{\text{hip fracture|no osteo|community}} * rr_{\text{hip fracture|osteo|no previous}}$$

$$P_{\text{hip fracture|previous|community}} = P_{\text{hip fracture|no osteo|community}} * rr_{\text{hip fracture|osteo|no previous}} * rr_{\text{hip fracture|osteo|previous}}$$

$$P_{\text{hip fracture|no osteo|LTC}} = P_{\text{hip fracture|no osteo|community}} * rr_{\text{hip fracture|LTC}}$$

$$P_{\text{hip fracture|osteo|no previous|LTC}} = P_{\text{hip fracture|no osteo|community}} * rr_{\text{hip fracture|osteo|no previous}} * rr_{\text{hip fracture|osteo|previous}} * rr_{\text{hip fracture|LTC}}$$

As with mortality, the above equations (equations 9 and 12-16) can be combined and then rearranged such that all the known factors are on one side of the equation and the only
unknown factor (\(P_{\text{hip fracture|no osteo|community}}\)) is on the other side leading to the sole solution which will allow replication of the population level data (equation 17).

\[
P_{\text{hip fracture|no osteo|community}} = \frac{P_{\text{hip fracture|all}}}{(\text{prop}_{\text{community}} - \text{prop}_{\text{osteo|community}}) + \text{rr}_{\text{hip fracture|osteo|no previous}} * (\text{prop}_{\text{osteo|community}} - \text{prop}_{\text{previous|community}}) + \text{rr}_{\text{hip fracture|osteo|previous}} * \text{prop}_{\text{previous|community}} + \text{rr}_{\text{hip fracture|LTC}} * (1 - \text{prop}_{\text{community}} - \text{prop}_{\text{osteo|LTC}}) + \text{rr}_{\text{hip fracture|osteo|no previous}} * \text{rr}_{\text{hip fracture|osteo|previous}} * \text{prop}_{\text{previous|LTC}} + \text{rr}_{\text{hip fracture|LTC}} * \text{prop}_{\text{previous|LTC}}}
\]
2. Convergent Validity

Table A1 details the results of the calibration exercise and highlights the convergent validity of the model in that it replicates key population level data.

It is clear that the probability of fracture in the general population of women is higher than the estimate for the population of non-osteoporotic community living women and that the difference increases with age. For hip fracture, the probability of fracture for a woman aged 80 who is not osteoporotic is 72% lower than for the general population estimate. Thus, analysis which does not allow for the prevalence of both fracture and living in LTC will lead to biased estimates of both the probability of fracture and fracture related death and consequently biased estimates of the effectiveness and cost effectiveness of treatments to prevent fracture.

Table A1 Results of Tests for Convergent Validity

| Transition probabilities | Probability based on general population data | Probability for non-osteoporotic and community living | Average probability across total population |
|--------------------------|---------------------------------------------|-----------------------------------------------------|-------------------------------------------|
| Death aged 65-69         | 0.0091                                      | 0.0084                                              | 0.0091                                    |
| Wrist Fracture aged 65-69| 0.0062                                      | 0.0055                                              | 0.0062                                    |
| Spine Fracture aged 65-69| 0.0015                                      | 0.0012                                              | 0.0015                                    |
| Hip Fracture aged 65-69  | 0.0018                                      | 0.0009                                              | 0.0018                                    |
| Death aged 70-74         | 0.0150                                      | 0.0144                                              | 0.0150                                    |
| Death aged 75-79         | 0.0254                                      | 0.0232                                              | 0.0254                                    |
| Wrist Fracture aged 70-79| 0.0086                                      | 0.0077                                              | 0.0086                                    |
| Spine Fracture aged 70-79| 0.0039                                      | 0.0027                                              | 0.0039                                    |
| Hip Fracture aged 70-79  | 0.0024                                      | 0.0009                                              | 0.0024                                    |
| Death aged 80-84         | 0.0443                                      | 0.0371                                              | 0.0443                                    |
| Death aged 85-89         | 0.0789                                      | 0.0648                                              | 0.0789                                    |
| Death aged 90+           | 0.1772                                      | 0.1592                                              | 0.1772                                    |
| Wrist Fracture aged 80+  | 0.0076                                      | 0.0057                                              | 0.0076                                    |
| Spine Fracture aged 80+  | 0.0076                                      | 0.0046                                              | 0.0076                                    |
| Hip Fracture aged 80+    | 0.0064                                      | 0.0018                                              | 0.0064                                    |
3. Internal and External Validation

The model was subject to rigorous internal validation. As part of the work on the CADTH health technology assessment, the model was subject to tests for coding accuracy. Subsequently, the revised version of the model was subject to similar testing and the mathematical logic of the model was tested by changing each parameter estimate in turn and checking that it gave the expected change in expected outcomes.