INVESTIGATING THE IMPACT ON MEDICINES ADHERENCE AND CLINICAL PRACTICE OF THE 2015 PREVENTING FRACTURES: WHERE TO START WITH OSTEOPOROSIS PROGRAM

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Independent, not-for-profit and evidence based, NPS enables better decisions about medicines and medical tests. This report is funded by the Australian Government Department of Health.

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CONTENTS

EXECUTIVE SUMMARY

This report documents changes in adherence to osteoporosis medicines before and after the NPS MedicineWise 2015 *Preventing fractures: where to start with osteoporosis* national multifaceted behaviour change program (referred to here as the 2015 Osteoporosis program), developed and delivered with funding received under the Quality Use of Medicines (QUM) Grant Agreement. Under the current QUM Grant Agreement (2019–22), NPS MedicineWise is required to measure the impact of grant-funded activities using outcome evaluations, including adherence studies.

The 2015 Osteoporosis program had a strong focus on treatment adherence. A clinical objective of the program was to improve adherence (10% relative increase in the proportion of adults who adhere to their prescribed medicines for osteoporosis).

There is evidence that, in Australia, patients with osteoporosis are not being managed optimally in primary care.[1] Despite an ageing population, the total number of prescriptions for commonly used osteoporosis medicines has remained stable in Australia since 2007 even though trends suggest that use of medicines for osteoporosis should be increasing. Further to under prescribing, poor medicines adherence is the main reason for poor response to treatment.[2]

Bisphosphonates and denosumab are the most commonly used first-line medicines for the treatment of osteoporosis in Australia.[3] The oral bisphosphonates are taken daily, weekly or monthly, with each dispensing lasting a month. Denosumab is given as a subcutaneous injection every 6 months. Poor adherence to treatment is a leading cause of fractures and hospitalisation and it has been estimated that 40% of Australians taking bisphosphonates do not meet the levels of adherence needed for therapeutic benefit.[4,5] Emerging data also raises concern about increased fracture risk shortly after discontinuation of denosumab, which should not be discontinued without considering a substitute treatment.[6]

To assess changes in adherence to osteoporosis medicines, we undertook a retrospective, observational study using interrupted time series (ITS) analysis. The study assessed changes in adherence to osteoporosis medicines before and after the 2015 Osteoporosis program, which ran from 1 October 2015 to 31 August 2016 (11 months). The ITS analysis used a 10% sample of Pharmaceutical Benefits Scheme (PBS) dispensing data for patients aged 45 years or older. Adherence was measured using the percentage of patients with a proportion of days covered (PDC) ≥ 80%.

- As an average script for oral bisphosphonates (including repeats) or denosumab lasts 6 months, any potential impact of the Osteoporosis program on the behaviour of consumers filling scripts might be subject to a lag if they did not visit their GP during the intervention period. For this reason, we assumed the Osteoporosis program came into effect 6 months post program launch, from 1 May 2016. Adherence rates were measured at two different time intervals after the intervention:
    - 1 May 2017, 12 months after the Osteoporosis program was assumed to come into effect.
    - 31 December 2019, 44 months after the Osteoporosis program was assumed to come into effect.

Key findings of the study include:

1. The clinical objective of the program, with respect to improving adherence by 10%, was exceeded, with an 11.3% relative increase in adherence within 12 months from the date the program was assumed to come into effect. There was a further increase in adherence by the end of the study period with an absolute increase of 16.6% and relative increase in adherence of 46.5%.

2. Adherence was improved in all three patient populations assessed in this study. Specifically:
    i) the all osteoporosis study population, which also included patients who switched osteoporosis medicines;
    ii) patients taking denosumab only; and
    iii) patients taking oral bisphosphonates only.
3. The increase in adherence for all patient populations was statistically significant at both the 12-month time point and at the end of the study period. The statistical significance, expressed in the form of p-values was $p=0.0045$ for the all osteoporosis study population, and $p<0.0001$ for the patients taking denosumab only and patients taking oral bisphosphonates only.
4. For the all osteoporosis study population, adherence increased from 47.6% 1 month before the program commenced to 52.4% at the end of the study period (31 December 2019). ITS modelling suggested that, without the program, the adherence rate would have fallen to 35.8% at this time point.
5. For the denosumab only population, adherence increased from a predicted value of 63.6% without the intervention to 65.0% with the intervention at the 12-month time point. This was not unexpected, given the higher baseline adherence rate in this patient population the month before the program started, and given that denosumab is administered less frequently than other osteoporosis medicines (every 6 months). By the end of the study period there was an absolute increase of 4.7% and relative increase in adherence of 7.7%.
6. The proportion of patients in the oral bisphosphonates only population, who were adherent within 12 months of the date the program was assumed to come into effect, increased from a predicted rate of 27.8% without the program to 30.3% with the program. By the end of the study period there was an absolute increase of 8.5% and relative increase in adherence of 41.5%.
7. For all patient populations, ITS analysis suggested that the effect of the program on improving adherence increased over time. This suggested that the program messages may have taken time to be implemented in clinical practice.

INTRODUCTION

1.1. Background

This report provides an analysis of changes in the rate of adherence to osteoporosis medicines following the NPS MedicineWise 2015 Osteoporosis program, developed and delivered with funding received under the QUM Grant Agreement.

Adherence is typically defined as the extent to which a patient takes a medicine according to the instructions prescribed to them by their healthcare provider.[7] Poor adherence to medicines can lead to poorer health outcomes. Poor adherence is an ongoing, significant QUM issue in Australia.

Under the QUM Grant Agreement, NPS MedicineWise delivers programs and interventions that seek to improve medicines adherence in areas of high-volume prescribing. Evaluation is an important step in ascertaining the effectiveness of these programs. Evaluation can provide insights that support improvements in future QUM behaviour change programs and may inform other levers for change across the sector.

1.2. The Osteoporosis program

Osteoporosis is a condition that causes bones to become weak and fragile so that even minor accidents can cause fractures. Such fractures are often referred to as 'minimal trauma fractures' or 'fragility fractures'. The condition is asymptomatic, often remaining undiagnosed until a person presents with a fracture. Around 6% of men and 23% of women in Australia aged over 50 years have osteoporosis and prevalence increases with age.[8] Bone fractures related to osteoporosis:

- reduce quality of life due to ongoing pain
- increase the chance of disability, loss of function and independence
- may ultimately lead to premature death [9].

Better adherence to osteoporosis medicines has been shown to prevent fractures related to osteoporosis.

The 2015 Osteoporosis program was launched on 1 October 2015. Educational visiting for the program ran until 31 August 2016 (11 months). The 2015 Osteoporosis program built on two prior NPS MedicineWise QUM programs: the 2007 large multifaceted program that involved educational visits to GPs and the 2011 non-visiting program. The 2015 Osteoporosis program differed from the previous programs in that it had a stronger focus on treatment adherence, with a key clinical objective being to increase by 10% (defined as a 10% relative increase in adherence by consumers) the proportion of adults who adhere to their prescribed medicines for osteoporosis.[2]

Active and passive educational activities were developed for this program, and included one-to-one educational visits, small group case-based meetings, and an online case study. The main target audience for the program was health professionals. Products to support the program goals included a GP-mediated consumer tool, which was designed to encourage patient adherence to prescribed osteoporosis medicines, specialist videos, and online knowledge hubs. The program attracted 7193 GPs to participate in educational visits or small group case-based meetings. In addition, a total of 536 nurses, 265 GPs and 684 pharmacists completed an online case study.

For health professionals, the key messages relating to adherence were:

- Medicines for osteoporosis vary markedly: consider effectiveness, tolerability, co-morbidities, and patient preferences when choosing therapy.
- Review therapy regularly for adherence, safety and suitability.

For consumers, the key message was:

- By taking your medicines for osteoporosis as prescribed you can strengthen your bones and reduce the chances of them breaking.

1.3. Study aims

This study aimed to:

- evaluate the impact of the 2015 Osteoporosis QUM program on medicine adherence.

1.4. Research questions

The specific research questions addressed in the study were:

1. Did the 2015 Osteoporosis program have an impact in improving the rate of adherence to osteoporosis medicines compared to no intervention?
2. If the 2015 Osteoporosis program did have an impact in improving the rate of adherence to osteoporosis medicines, what was the impact per medicine class for the most commonly used first-line medicines for the treatment of osteoporosis in Australia?

The first research question was designed to evaluate the impact of the 2015 Osteoporosis program on the all osteoporosis study population, including patients who switched osteoporosis medicines. The second question was designed to:

1) examine if the Osteoporosis program had the same magnitude of impact on adherence rate among patients in different medicine classes, using the two most commonly used medicine classes as an example; and
2) confirm the assumption that a treatment break should be considered as non-adherence in this study (see section 1.5.5 for more details on treatment break).

1.5. Methods

1.5.1. Study design

This was a retrospective, observational study, using interrupted time series (ITS)[10] analysis of a 10% sample of Pharmaceutical Benefits Scheme (PBS) data to assess the impact of the Osteoporosis program in improving adherence to osteoporosis medicines.

1.5.2. Data sources

The 10% PBS dataset was used to assess adherence. The 10% PBS dataset, which provides information on when patients had their prescriptions dispensed, is often used by researchers to help estimate patient adherence to medicines. MedicineInsight data was not used for this analysis because these (MedicineInsight) data contain information on medicines prescribed rather than medicines dispensed. As not all medicines prescribed are dispensed, and in the absence of any current linkage of MedicineInsight data with PBS data, use of dispensing data was considered to be the best data source for this analysis.

The 10% PBS sample is a random 10% sample of PBS claims data for Australians. The data contains patient-level administrative information about each PBS prescription dispensed. The data includes information on patient demographics (year of birth, sex, year of death), information on the medicines dispensed (eg, type of script – original or repeat, PBS item code, quantity dispensed, concessional status, number of repeats, date of prescribing, date of supply, pharmacy state, prescriber ID, prescriber type). Prescription data on under co-payment paid by the patients are available from 1 April 2012. The PBS 10% sample does not provide information on diagnoses, outcomes or tests. The 10%

PBS sample includes prescribing data from all prescribers, including non-GPs, who were not recipients of the Osteoporosis program.

NPS MedicineWise received approval from the Services Australia External Request Evaluation Committee (EREC) for the use of this dataset for this project.

1.5.3. Study period

The 2015 Osteoporosis program was conducted (started and delivered in the field) from 1 October 2015 to 31 August 2016. The period of time analysed for the adherence study covered approximately 9 years from 1 December 2011 to 31 December 2019. This timeframe was selected for the following reasons:

- To separate the dilution of effects of the two previous programs (2007 and 2011 programs); and
- To separate the potential confounding effects of the COVID-19 pandemic.
- The dataset prior to the 1 December 2011 was in a different format and could not be reconciled with the current dataset within the given timeframe. Thus, the 1 December 2011 was selected as the start date.

1.5.4. Study population

Two population groups were formed for this study: 1) the general study population and 2) the all osteoporosis study population. The general study population was used to calculate the overall osteoporosis prevalence and the prevalence by sub-group. The all osteoporosis study population, drawn from the general study population, was used for the data analysis to answer the research questions.

The general study population

The general study population included patients who met the following inclusion criteria:

- Valid information recorded for age and sex.
- Aged 45 years or older on 1 December 2011.

Patients with a birthdate in the 1800s and/or with an unknown sex recorded, were discarded. During the study period, patients who died were treated as censored in the year of their death. Therefore no 'exclusion' criterion was applied for patients who deceased.

Patients were excluded from the study if they were 44 years or younger at the start of the study for consistency with a previous study on osteoporosis treatment.[11] As osteoporosis is predominantly diagnosed in people aged ≥ 50 years of age, restricting the study population to patients aged 45 years or older provides a buffer window, also capturing patients with an early diagnosis of osteoporosis.

The all osteoporosis study population

The all osteoporosis study population included patients from the general study cohort who had:

- a record of an osteoporosis medicine being dispensed during the study period. This was used as a proxy to identify a patient with osteoporosis
- a minimum of 12 months of follow-up data following the first record of dispensing of an osteoporosis medicine within the study period. This is because the outcome (proportion of days covered [PDC]) could be calculated only for patients who had more than one prescription dispensed.

Patients were censored from the study at the:

- end of the study period (31 December 2019); OR

- year when the patient died. However, data prior to death was included in the analysis.

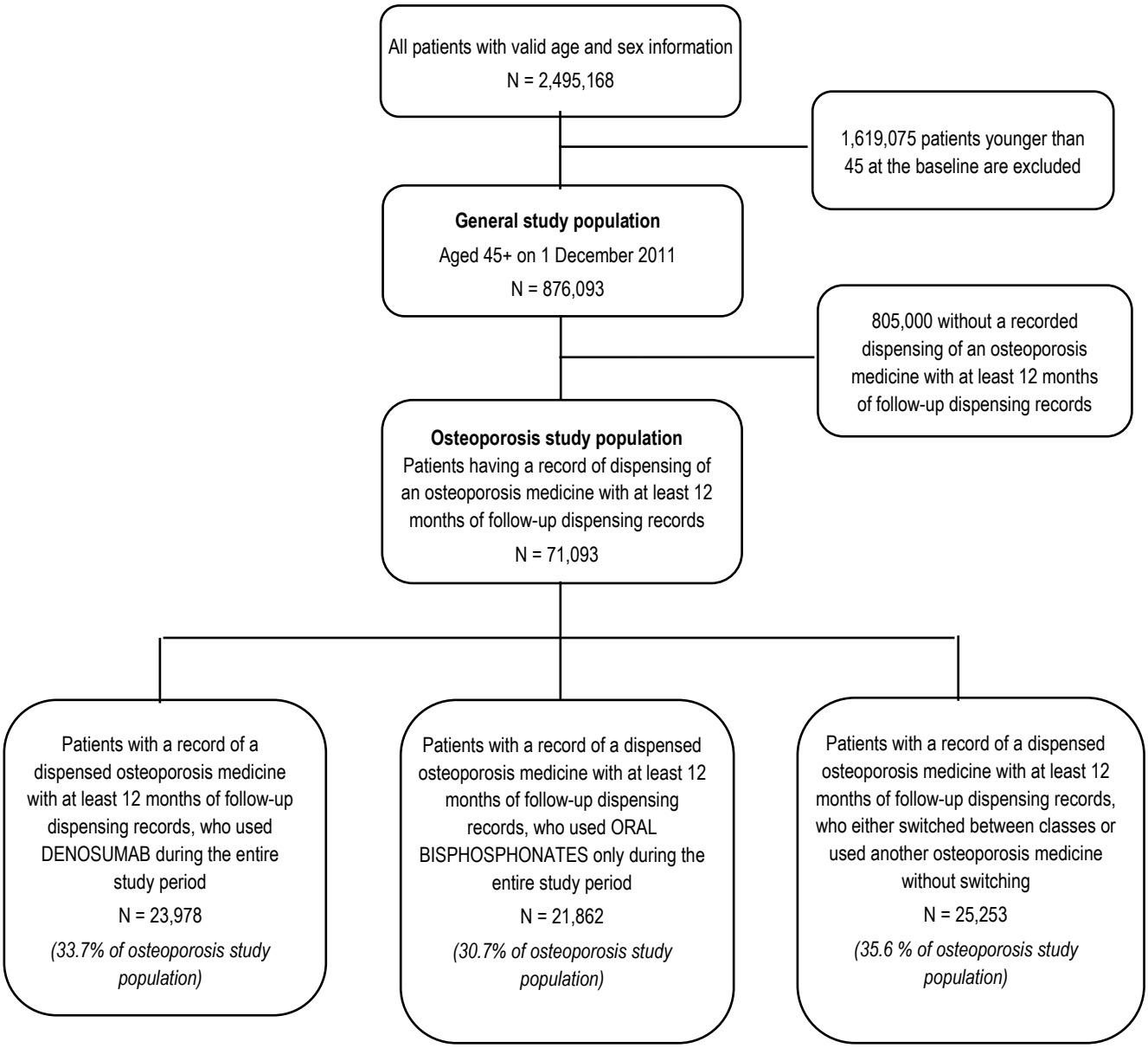
Patients were defined as having a dispensing record for an osteoporosis medicine if they had at least one dispensing record containing one of the following medicine classes (or related biologics) during the study period:

- Group 1: Denosumab
- Group 2: Oral bisphosphonates:
  - Bisphosphonates single: alendronate, risedronate
  - Bisphosphonate combinations including with colecalciferol and/or calcium carbonate
- Group 3: Raloxifene or teriparatide
- Group 4: Strontium ranelate
- Group 5: Zoledronic acid.

The Anatomical Therapeutic Chemical (ATC) codes and medicine names presented in Appendix 1 were used to identify dispensing of osteoporosis medicines.

A total of 876,093 patients formed the general population cohort and a total of 71,093 formed the all osteoporosis study population, as depicted in Figure 1.

Figure 1: **PATIENT INCLUSION PROCESS**



1.5.5. Study outcome definitions

Two terms are commonly used in the literature to describe the extent to which a patient uses medicines in the treatment of chronic diseases as prescribed: compliance and persistence. Compliance is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen, and persistence as the duration of time from initiation to discontinuation of therapy. Adherence as a general term encompasses both persistence and compliance.[12] Because compliance and persistence are distinct albeit overlapping components, for the context of this study we used the encompassing measure of adherence that incorporates both compliance and persistence. (The way that we handled treatment break/discontinuation is discussed below).

The primary objective of the study was to measure long-term adherence with osteoporosis treatment. Adherence was quantified by calculating the PDC,[13] which measures the percentage of time that the prescribed medicine is available to a patient. The PDC was calculated as the number of days covered by the dispensed medicine in units, divided by the number of assumed therapy days within the

observational period. Assumed therapy days represents a time interval from the date of the first prescription dispensing to the date of the last prescription dispensing plus last prescription supply (eg, 180 days for denosumab and 30 days for oral bisphosphonates). The PDC could only be calculated for patients who had more than one prescription dispensed during the study period. Applying the most commonly used cut-off point, patients were classified as adherent when their PDC was ≥ 80% and non-adherent with a PDC < 80%.[14,15]

The ITS model used PDC calculated on a monthly basis. Monthly PDC was calculated by dividing the total number of days covered by the dispensing of an osteoporosis medicine in each month by the total number of days in that month, capped at 100%. For example, consider a patient with a dispensing record of denosumab on 5 May 2016 and a subsequent dispensing record of denosumab on 20 November 2016 (200 days). As the treatment duration for denosumab is 180 days, the PDCs for the months of May 2016 to October 2016 for this patient were 100%. However, the PDC for the month of November 2016 would be calculated as only 33% because the refill gap is 20 days. That is, to maintain 100% adherence, the patient needed to refill the prescription on 1 November 2016.

The methodology for calculating the PDC accounted for the specificity of treatment including variation in duration, medication switching and overlapping.

- Variation in treatment duration: To calculate days covered, the quantity of medicine dispensed was assumed to be the maximum amount allowed in the Schedule for each type of osteoporosis medicine (see Appendix 2, Table 15 – Expected duration of therapy for osteoporosis medicines). The expected duration of therapy was aligned with the maximum quantity dispensed. For example, the expected duration of therapy for denosumab was assumed to be 180 days; 28 days for the oral bisphosphonate (alendronate); and 360 days for zoledronic acid.
- Medication switching: Nearly one-third (27.9%) of patients with osteoporosis switched osteoporosis medicines during the course of their treatment during the study period. All patients were included in the analysis, even if they switched therapy. All medicines listed in Appendix 1 were considered when calculating PDC.
- Crediting overlapping days' supply: There were many instances where a patient refilled their prescription before exhausting the previous fill. For example, one patient had a second claim, on 30 July 2015, which occurred before the end of the previous claim's supply (5 August 2015). In this instance, the number of days covered by each medicine was accumulated and factored into the PDC calculation. This was done by shifting the fill date of the subsequent fill forward by the number of overlapping days.

To transform the data into a structure required for ITS analysis, the patient-level monthly adherence classification (adherent vs nonadherent) was aggregated to create the monthly rate of adherence for the entire osteoporosis study population. To calculate the monthly aggregated rate of adherence, the denominator was the number of patients who had data in that month, and the numerator was the number of patients in that month who were classified as 'adherent'. For example, for the month of May 2016, the denominator was 68,000 patients who had PBS data in May 2016 and who were alive, and the numerator was 34,000 patients who were classified as adherent in that month. As such, the rate of adherence for the entire osteoporosis study population for the month of May 2016 was 34,000/68,000 = 50.0%. The monthly denominator changed over time depending on the number of patients who died, and the number of new patients identified.

Most PBS prescription dispensing provides a quantity sufficient for 1 month of therapy, however prescriptions for zoledronic acid and denosumab cover 12 months and 6 months, respectively. Therefore, the monthly PDCs from the date of the first dispensing for 6 months for denosumab and for 12 months for zoledronic acid were consistently 100%. Keeping individual patients' data in the analysis for the first 6–12 months would bias the underlying trend of the ITS model, since all patients would appear to be less adherent in the subsequent 6–12 months. To remove this bias, the first 12 months of PDC data for every patient was removed before aggregation of the PDC data for the ITS

analysis. As such, the actual dataset in which the ITS modelling was performed starts from December 2012.

Handling of treatment break

As per the clinical guideline for treating osteoporosis, treatment breaks may be included in the long-term management plan if:

(1) the patient has been treated with a bisphosphonate or zoledronic acid

(2) the disease is less severe

(3) the response to treatment has been satisfactory, and

(4) the risk of future fracture is estimated to be low.[16,17]

For this study a 'treatment break', including all refill gaps, was categorised as 'non-adherence'. This approach was selected because:

1. The concept of a 'treatment break' was only relevant for oral bisphosphonates and zoledronic acid,[16] which in combination comprise approximately 51% of the total number of dispensing records. Oral bisphosphonates as a class, were the most commonly used group of medicines, accounting for approximately 45% of dispensing records, and denosumab was the most commonly prescribed medicine, accounting for approximately 41% of the dispensing records. For denosumab, as per treatment guidelines,[8] discontinuation is not recommended due to the rapid off-treatment effects. Discontinuation of denosumab should be followed by a bisphosphonate.
2. Data (such as clinical notes) to help distinguish between 'treatment break' and 'non-adherence' was not available for the 10% PBS data.

The assumption that a treatment break equates to non-adherence will result in some underestimation of the adherence rate. However, this underestimation is likely to be minimal given that:

- results from a qualitative study conducted in 2018[18] suggest that, while most GPs are aware of the concept of a treatment break for patients taking or using bisphosphonates, only some would consider it for those with a good response to therapy after 5 years
- the concept of a treatment break is only relevant for oral bisphosphonates and for zoledronic acid (51% of the study population)
- according to the latest treatment guidelines from Healthy Bones Australia, a treatment break is generally not recommended at all[19]
- a treatment break should only be considered after 5 to 10 years in postmenopausal women and men over 50 years of age with osteoporosis who have responded well to treatment (T-score of ≥−2.5 and no recent fractures), based on the Royal Australian College of General Practitioners osteoarthritis (RACGP/OA) guidelines. The RACGP/OA guidelines also state that treatment should be continued if bone mineral density (BMD) remains low (T score of <−2.5) and/or if there are incident vertebral fractures.[20]

Further, as the 2015 Osteoporosis program did not result in a change in the median level of agreement by GPs with the statement that, "It is appropriate to routinely suspend treatment after 5 years in all patients", it is likely that the general perception of a treatment break remained consistent before and after the program. The absolute increase in adherence calculated from the Osteoporosis program is therefore likely to be a true reflection of increased adherence, and not a reflection of changes in the rate of recommendation of treatment breaks.[2]

1.5.6. Intervention terms

Educational visiting for the Osteoporosis program was delivered between 1 October 2015 and 31 August 2016. Adherence to osteoporosis medicines was calculated using a 10% sample of PBS dispensing data. As an average script for oral bisphosphonates (including repeats) or denosumab lasts 6 months, any potential impact of the osteoporosis program on the script-filling behaviour of consumers might be subject to a lag if they did not visit their GPs during the intervention period. For this reason, it was assumed the Osteoporosis program came into effect 6 months post program launch, on 1 May 2016.

Three functions or terms (step, trend, and a combined step and trend) were considered in our approach to modelling the effect of the Osteoporosis program on adherence with osteoporosis medicines. A step function assumes that the event (Osteoporosis program) had an immediate and constant impact after coming into effect, whereas a trend function assumes that the event had a gradual, either increasing or decreasing, changing impact after program launch. A combined step and trend function assumes that the event had an immediate and long-term impact, and this impact had a gradual trend (either increasing or decreasing) after program launch.

1.5.7. Statistical methods

ITS modelling, also known as intervention modelling, is the gold standard approach for assessing impact with population-level intervention programs in public health in the absence of a randomised controlled trial.[10] ITS is a quantitative, statistical method in which multiple repeated observations are made at regular intervals before and after an intervention (the 'interruption' in the time series). Statistical analysis is performed to determine whether there is a change in the observations, or trend of observations, following an intervention.

ITS models provide the following key outputs when estimating the impact of an intervention or event:

1. A time series model is fitted to the monthly observational data of interest, ie, the rate of adherence (referred to as the 'actual' series).
2. The time series model forecasts what the rate of adherence would have been had the intervention program or event not taken place (referred to as the 'counterfactual series').
3. The two series are then compared ('counterfactual' vs 'actual') to obtain a quantifiable change in the rate of adherence.

A full description of ITS methodology is provided in Appendix 3. We considered different functional forms of the Osteoporosis program intervention terms and accounted for features of the data including the underlying trend and any potential seasonality or autocorrelation.

At each iteration of the model building process, model fit criteria, such as Akaike Information Criteria (AIC) and model residuals were examined.[21] The AIC is an estimator of prediction error. It also estimates the quality of each model, relative to other iteration models, providing a means for model selection. Lower AICs indicate better fitting models. Model residuals were examined to ensure concordance with time series modelling assumptions, including normality of residuals and no remaining autocorrelation.

To examine the impact of the program on the percentage of patients with a PDC ≥ 80%, the best fitting model for the data covering the study period 1 December 2012 to 31 December 2019 was identified. The response variable was binary, however this was approximated to be normal because the monthly sample sizes for each dataset were large enough with the average monthly sample size for the general study population, oral bisphosphonates and denosumab cohorts (45,219.98, 14,579.49 and 10,448.02, respectively).

The impact of the Osteoporosis program was assessed by comparing the estimated adherence rates at two time points (on 1 May 2017, 12 months after the Osteoporosis program was assumed to come into effect, and on 31 December 2019, the end of the study period). These time points reflect the

scenario in which the Osteoporosis program did take place (observed scenario), and the scenario where the program did not take place (counterfactual/hypothetical scenario).

1.6. Results

1.6.1. Sample description

During the study period (1 December 2011 to 31 December 2019) a total of 876,093 patients fit the criteria for the general study population. From this general study population, 71,093 patients fit the criteria for the all osteoporosis study population.

The all osteoporosis study population consisted of individual patients who filled more than one osteoporosis script over the study period. Within this study cohort of patients aged 45 years or older, this translated to an overall prevalence rate of people receiving osteoporosis treatment of 8.11%. Basic characteristics of the study cohort are summarised in Table 1.

When stratified by gender, the prevalence of osteoporosis in the study patients was 3.40% for men and 12.53% for women aged 45 years or older. Most of the patients with osteoporosis lived in the three largest states in Australia, with 38.5% of patients from New South Wales (NSW), 22.8 % from Victoria and 19.6% from Queensland. The majority of patients were aged between 60 and 84 years, and most (81.0%) were concessional patients, which was expected given that osteoporosis is more prevalent among the elderly population.

Demographic details for patients included in the general study and the all osteoporosis study populations are detailed in Table 1.

Table 1: **DEMOGRAPHIC CHARACTERISTICS, FREQUENCY DISTRIBUTIONS, GENERAL STUDY POPULATION AND THE ALL OSTEOPOROSIS STUDY POPULATION, DECEMBER 2011–DECEMBER 2019**

Patient characteristics	General study population, N (a)	General study population, % (b)	Patients with osteoporosis prescription dispensed, N (c)	Patients with osteoporosis prescription dispensed, % (d)	Prevalence rate % (e = c/a)
Total	**876,093**	**100.00**	**71,093**	**100.00**	**8.11**
Sex					
Male	423,346	48.32	14,376	20.22	3.40
Female	452,747	51.68	56,717	79.78	12.53
Age (years)					
45–49	156,801	17.9	1,441	2.03	0.92
50–54	152,404	17.4	3,510	4.94	2.30
55–59	137,491	15.69	5,635	7.93	4.10
60–64	126,161	14.4	8,381	11.79	6.64
65–69	98,936	11.29	11,653	16.39	11.78
70–74	73,990	8.45	12,461	17.53	16.84
75–79	55,804	6.37	12,062	16.97	21.61
80–84	42,892	4.9	10,003	14.07	23.32
85–89	23,511	2.68	4,953	6.97	21.07
90–94	7,017	0.8	942	1.33	13.42
≥95	1,086	0.12	52	0.07	4.79
State					
ACT	22,764	2.6	968	1.36	4.25
NSW	317,262	36.21	27,055	38.06	8.53
NT	10,088	1.15	182	0.26	1.80
QLD	169,799	19.38	13,947	19.62	8.21
SA	66,241	7.56	5,464	7.69	8.25
TAS	20,385	2.33	1,554	2.19	7.62
VIC	190,924	21.79	16,237	22.84	8.50
WA	78,118	8.92	5,686	8	7.28
Unknown	512	0.06	0	0	n/a
Concessional status					
Concessional	293,429	33.49	57,589	81.01	19.63
General	580,079	66.21	13,504	18.99	2.33
Unknown	2,585	0.3	0	0	n/a

1.6.2. Impact of the Osteoporosis program (all osteoporosis study population)

A stepwise model building process was undertaken using different forms of the 2015 Osteoporosis program intervention term to evaluate the impact of the program on adherence. As indicated in Figure 1, the overall sample size of the osteoporosis population was 71,093 patients. The model fit criteria for the final models for each of the functional forms of the program intervention term are presented in Table 2.

The use of a trend function to model the intervention term provided the best fit to the data for patients in the all osteoporosis study population. There was demonstrated evidence (p = 0.0045) of an increase in the rate of adherence with osteoporosis medicines as a result of the program.

Table 2: **SUMMARY OF TESTING INTERVENTION TERMS, ALL OSTEOPOROSIS STUDY POPULATION**

2015 Intervention function	2015 Intervention coefficient estimate (p-value)	AIC	Standard error
Step	0.00077316 (0.8818)	-611.152	0.005838
Trend	**0.00377118 (0.0045)**	**-636.305**	**0.005112**
Step and Trend	0.00004313, 0.00364552 (0.0006) *	-631.197	0.0053

* p-value based on Chi-squared statistic from a likelihood ratio test jointly testing all intervention variables.

AIC = Akaike information criterion.

Residual diagnostics from the final trend model, presented in Table 3, demonstrated that autocorrelation was adequately accounted for. Parameter estimates for the final trend model that fit the data for the all osteoporosis population are presented in Table 4.

Table 3: **RESIDUAL DIAGNOSTICS FROM FINAL MODEL, ALL OSTEOPOROSIS STUDY POPULATION**

Model	Normality (p-value) Shapiro-Wilk	Autocorrelation check (p-value) Lags 6, 12, 18, 24
Trend	0.825	0.5973, 0.1540, 0.2697, 0.4446

Table 4: **PARAMETER ESTIMATES FROM FINAL TREND MODEL, PROPORTION OF ADHERENT PATIENTS, ALL OSTEOPOROSIS POPULATION**

Parameter description	Estimate	Standard error	P-value
Intercept	0.65840016	0.03440032	<.0001
Trend	-0.0333615	0.00606431	<.0001
Intervention – trend	0.00377118	0.00132825	0.0045
Seasonal – January	-0.0080277	0.00289544	<.0001 ^
Seasonal – February	-0.0094976	0.00343935	
Seasonal – March	-0.0010518	0.00367783	
Seasonal – April	0.00112966	0.00366971	
Seasonal – May	-0.0031011	0.00348708	
Seasonal – June	0.00233736	0.00363806	
Seasonal – July	0.00462537	0.00367931	

Parameter description	Estimate	Standard error	P-value
Seasonal – August	0.00016259	0.00346811	
Seasonal – September	0.00107488	0.00295979	
Seasonal – October	-0.0041479	0.00193427	
Seasonal – November	Ref.**		
Seasonal – December	0.00749893	0.00192559	
MA1	-0.4075019	0.10671261	0.0001
MA6	-0.301587	0.10831704	0.0054
AR1	0.95780504	0.04366703	<.0001

^p-value based on Chi-squared statistic from a likelihood ratio test jointly testing all seasonal variables (January – December).

*** Ref. = reference: November is the reference dummy variable for seasonality.*

Estimated impact of the program – all osteoporosis population

Figure 2 provides a visualisation of the impact of the 2015 Osteoporosis program up to 31 December 2019, and the modelled rate of adherence to all osteoporosis medicines (red line) against the rate estimated to have occurred had the program not taken place (green line), using the trend model.

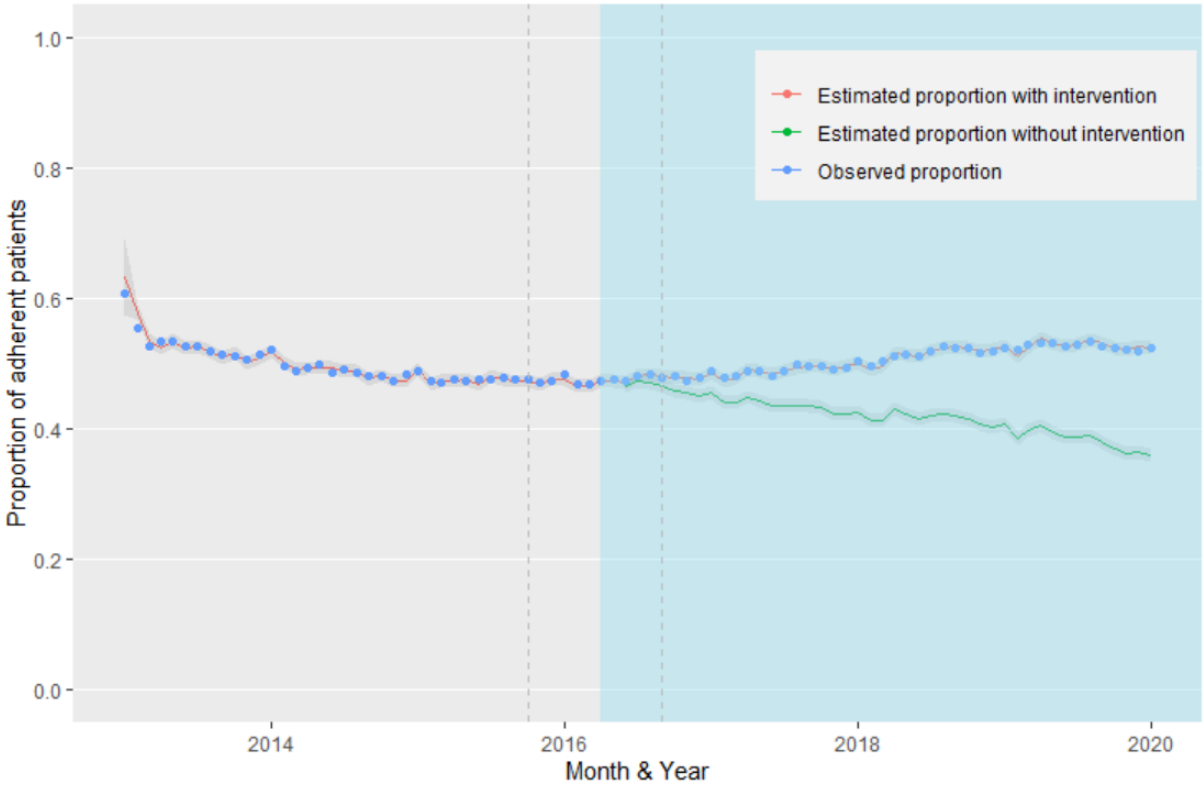
As illustrated in Figure 2, approximately 60.7% of patients aged 45 years or older adhered to their osteoporosis medicines, with a PDC of ≥ 80% at the start of the study period (1 December 2012). The adherence rate declined to approximately 46.7% in September 2015 (the month before program launch). The downward underlying trend of the time series of the adherence rate suggests that the longer the patients were taking osteoporosis treatment, the more their adherence declined. The decline could have been due to a range of possible factors, including ageing and the challenges associated with using life-long medicines.

Without the program, the model predicted that adherence would have fallen to 43.5% by May 2017 (12 months after the Osteoporosis program was assumed to come into effect). This compared to an estimated adherence rate of 48.4% with the program. At the end of the study period (31 December 2019, 44 months after the Osteoporosis program was assumed to come into effect), the adherence rate was estimated to be 52.4%, compared with 35.8% had the 2015 Osteoporosis program not taken place. The data at this time point for the observed proportion indicated that the adherence rate had started to taper slightly. To investigate this further, a decay model was fitted to the data, however the analysis showed that the trend model that had been selected initially was a better fit.

Table 5: **IMPACT OF THE 2015 OSTEOPOROSIS PROGRAM ON PROPORTION OF ADHERENT PATIENTS, ALL OSTEOPOROSIS POPULATION**

Time point	Model	Estimated adherent population without the program (95% CI)	Estimated adherent population with the program (95% CI)	Absolute increase in adherence	Relative increase in adherence
31 May 2017	Trend	43.5% (42.5%, 44.5%)	48.4% (47.4%, 49.4%)	4.9%	11.3%
31 Dec 2019	Trend	35.8% (34.8%, 36.8%)	52.4% (51.4%, 53.4%)	16.6%	46.5%

Figure 2: **ESTIMATED IMPACT OF THE OSTEOPOROSIS PROGRAM ON PROPORTION OF ADHERENT PATIENTS, ALL OSTEOPOROSIS POPULATION**



Note: The two dotted vertical lines indicate the time frame when the 2015 Osteoporosis program was delivered: from 1 October 2015 to 31 August 2016 (11 months)

1.6.3. Impact of the Osteoporosis program (denosumab only population)

A stepwise model building process was undertaken using different functional forms of the 2015 Osteoporosis program intervention term to evaluate the impact of the program on changing the rate of adherence for patients who were dispensed denosumab only. As indicated in Figure 1, the overall sample size of patients who were dispensed denosumab only was 23,978 patients (33.7% of the all osteoporosis study population). The model fit criteria for the final models for each of the functional forms of the program intervention term are presented in Table 6.

The use of a trend function to model the intervention term provided the best fit to the data for the denosumab only population. There was demonstrated evidence ($p < 0.0001$) of an increase in the rate of adherence with denosumab as a result of the program.

Table 6: **SUMMARY OF TESTING INTERVENTION TERMS, DENOSUMAB POPULATION**

2015 Intervention function	2015 Intervention coefficient estimate (p-value)	AIC	Standard error
Step	0.00797735 (0.0958)	-601.688	0.006261
Trend	**0.00106157 (<.0001)**	**-616.453**	**0.005802**
Step and Trend	0.00855156, 0.00103674 (<.0001) *	-612.53	0.005949

* p-value based on Chi-squared statistic from a likelihood ratio test jointly testing all intervention variables.

AIC = Akaike information criterion.

Residual diagnostics from the final trend model, presented in Table 7, demonstrated that autocorrelation had been adequately accounted for. Parameter estimates for the final trend model that fit the data for the denosumab only population are presented in Table 8.

Table 7: **RESIDUAL DIAGNOSTICS FROM FINAL MODEL, DENOSUMAB POPULATION**

Model	Normality (p-value) Shapiro-Wilk	Autocorrelation check (p-value) Lags 6, 12, 18, 24
Trend	0.988	0.4117, 0.6326, 0.8571, 0.8541

Table 8: **PARAMETER ESTIMATES FROM FINAL TREND MODEL, PROPOTION OF ADHERENT PATIENTS, DENOSUMAB POPULATION**

Parameter description	Estimate	Standard error	P-value
Intercept	0.76751072	0.0059275	<.0001
Trend	-0.0177121	0.00111754	<.0001
Intervention – trend	0.00106157	0.00018771	<.0001
Seasonal – January	0.0015536	0.00390877	<.0001 ^
Seasonal – February	0.008629	0.00444009	
Seasonal – March	0.0109459	0.00397232	
Seasonal – April	0.00945582	0.00331271	
Seasonal – May	0.0015812	0.00242687	
Seasonal – June	0.01044296	0.00340553	
Seasonal – July	0.02181039	0.0040355	
Seasonal – August	0.01010354	0.00444864	
Seasonal – September	0.00409101	0.00386423	
Seasonal – October	-0.0033269	0.00297678	
Seasonal – November	Ref. **		
Seasonal – December	0.00676721	0.00299736	
AR1	0.52411868	0.09176636	<.0001
AR3	-0.2769656	0.10041971	0.0058
AR6	0.39579989	0.10073762	<.0001

^p-value based on Chi-squared statistic from a likelihood ratio test jointly testing all seasonal variables (January – December).

*** Ref. = reference: November is the reference dummy variable for seasonality.*

Estimated impact of the program – denosumab population

Figure 3 provides a visualisation of the impact of the 2015 Osteoporosis program up to 31 December 2019, and the modelled rate of adherence with denosumab (red line) against the rate estimated to have occurred had the program not taken place (green line), using the final trend model.

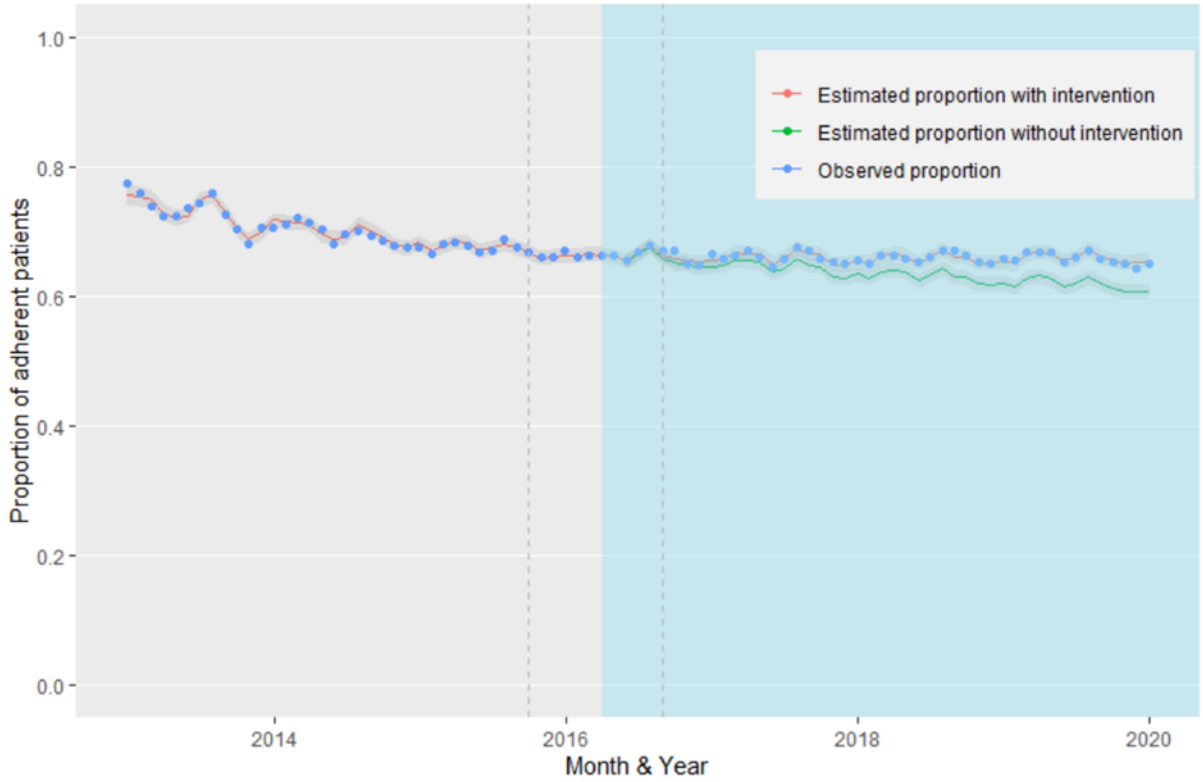
Among the denosumab population, approximately 77.3% were adherent at the start of the study period (1 December 2012). By September 2015 (the month before program launch), the adherence rate was estimated to have dropped to 66.7%. As shown in Table 9, at May 2017 (12 months after the Osteoporosis program was assumed to come into effect), the proportion of the denosumab population with a PDC ≥ 80% was estimated to be 65.0%. Had the 2015 Osteoporosis program not taken place, the adherence rate was estimated to have declined by this time point to 63.6%. At the end of the

study period (31 December 2019, 44 months after the Osteoporosis program was assumed to come into effect), the proportion of patients who were adherent to denosumab was estimated to be 65.4%. Had the program not occurred, the modelled adherence rate was estimated to be 60.7%.

Table 9: **IMPACT OF THE 2015 OSTEOPOROSIS PROGRAM ON PROPORTION OF ADHERENT PATIENTS, DENOSUMAB POPULATION**

Time point	Model	Estimated adherent population without the program (95% CI)	Estimated adherent population with the program (95% CI)	Absolute increase in adherence	Relative increase in adherence
31 May 2017	Trend	63.6% (62.5%, 64.8%)	65.0% (63.9%, 66.2%)	1.4%	2.2%
31 Dec 2019	Trend	60.7% (59.6%, 61.8%)	65.4% (64.2%, 66.5%)	4.7%	7.7%

Figure 3: **ESTIMATED IMPACT OF THE OSTEOPOROSIS PROGRAM ON PROPORTION OF ADHERENT PATIENTS, DENOSUMAB POPULATION**



Note: The two dotted vertical lines indicate the time frame when the 2015 Osteoporosis program was delivered: from 1 October 2015 to 31 August 2016 (11 months)

1.6.4. Impact of the Osteoporosis program (oral bisphosphonates only population)

A stepwise model building process was undertaken using different functional forms of the 2015 Osteoporosis program intervention term to evaluate the impact of the program on changing the rate of adherence to oral bisphosphonates only. As indicated in Figure 1, the overall sample size of patients taking oral bisphosphonates only was 21,862 patients (30.7% of the all osteoporosis study population). The model fit criteria for the final models for each of the functional forms of the program intervention term are presented in Table 10.

The use of a trend function to model the intervention term provided the best fit to the data for the oral bisphosphonates only population. There was demonstrated evidence ($p < 0.0001$) of an increase in the adherence rate for oral bisphosphonates as a result of the program.

Table 10: **SUMMARY OF TESTING INTERVENTION TERMS, ORAL BISPHOSPHONATES POPULATION**

2015 Intervention function	2015 Intervention coefficient estimate (p-value)	AIC	Standard error
Step	0.00136987 (0.7811)	-650.685	0.004712
Trend	**0.00193744 (<.0001)**	**-690.326**	**0.003613**
Step and Trend	-0.002321, 0.00207325 (0.0002)	-676.640	0.004055

* p-value based on Chi-squared statistic from a likelihood ratio test jointly testing all intervention variables.
AIC = Akaike information criterion.

Residual diagnostics from the final trend model, presented in Table 11, demonstrated that autocorrelation had been adequately accounted for. Parameter estimates for the final trend model that fit the data of the oral bisphosphonates only population are presented in Table 12.

Table 11: **RESIDUAL DIAGNOSTICS FROM FINAL MODEL, ORAL BISPHOSPHONATES POPULATION**

Model	Normality (p-value) Shapiro-Wilk	Autocorrelation check (p-value) Lags 6, 12, 18, 24
Trend	0.951	0.1094, 0.3030, 0.6100, 0.4372

Table 12: **PARAMETER ESTIMATES FROM FINAL TREND MODEL, PROPORTION OF ADHERENT PATIENTS, ORAL BISPHOSPHONATES POPULATION**

Parameter description	Estimate	Standard error	P-value
Intercept	0.60764292	0.00560088	<.0001
Trend	-0.0435708	0.00130889	<.0001
Intervention – trend	0.00193744	0.00015919	<.0001
Seasonal – January	-0.0119022	0.00230925	<.0001^
Seasonal – February	-0.0131009	0.00265894	
Seasonal – March	-0.0046553	0.00277901	
Seasonal – April	-0.0011225	0.0029973	
Seasonal – May	-0.0041922	0.00286575	
Seasonal – June	-0.0002726	0.00296773	
Seasonal – July	-0.0022636	0.00274497	
Seasonal – August	-0.0039899	0.00264598	
Seasonal – September	-0.0020717	0.00230109	
Seasonal – October	-0.0054509	0.00168652	
Seasonal – November	Ref. **		
Seasonal – December	0.00615443	0.00169128	
MA4	-0.3180606	0.10791289	0.0032
MA6	-0.2096199	0.10361952	0.0431
MA7	0.51420703	0.12537102	<.0001
AR1	0.79117012	0.06416985	<.0001

Parameter description	Estimate	Standard error	P-value
AR14	-0.2003651	0.06299903	0.0015

^p-value based on Chi-squared statistic from a likelihood ratio test jointly testing all seasonal variables (January – December).

*** Ref. = reference: November is the reference dummy variable for seasonality.*

Estimated impact of the program – oral bisphosphonates only population

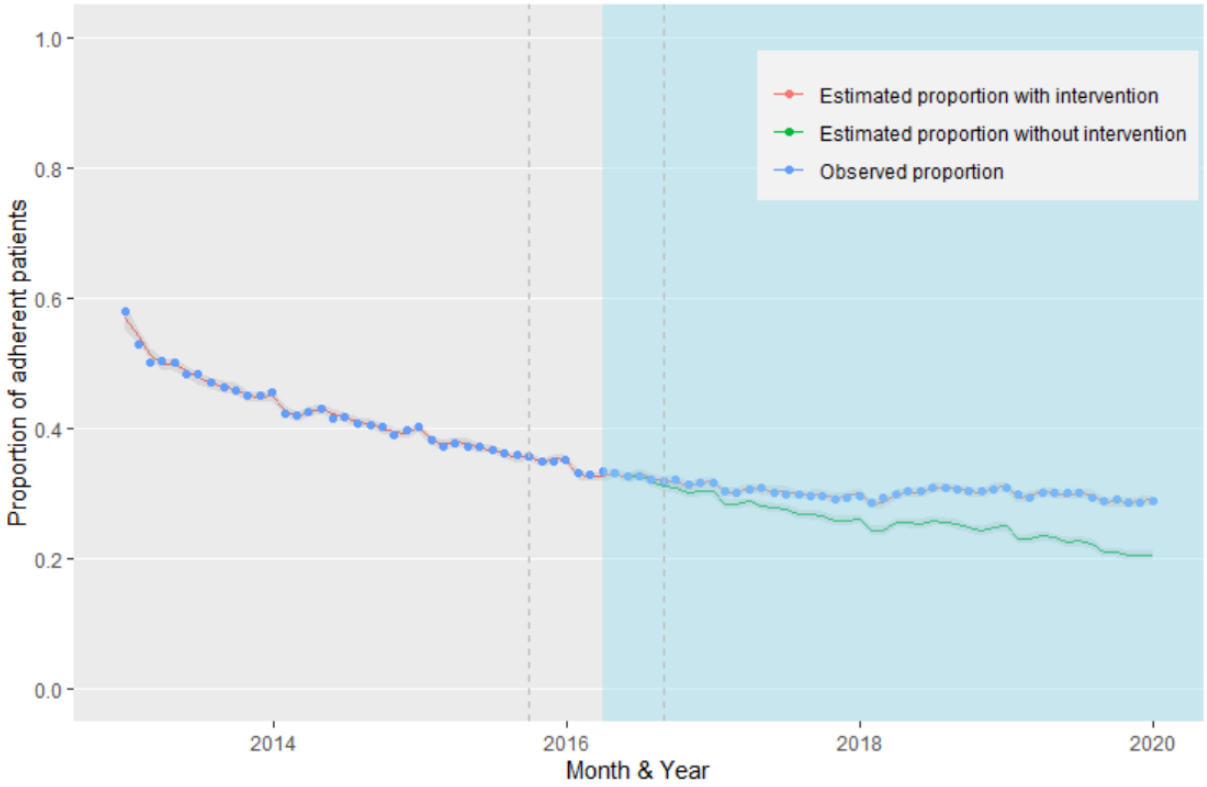
Figure 4 provides a visualisation of the impact of the 2015 Osteoporosis program up to 31 December 2019, and the modelled rate of adherence to oral bisphosphonates (red line) against the rate estimated to have occurred had the program not taken place (green line), using the final trend model.

Among the oral bisphosphonates only population, approximately 57.9% were adherent at the start of the study period (1 December 2012). By September 2015 (the month before program launch), the adherence rate was estimated to have dropped to 35.7%. As shown in Table 13, at May 2017 (12 months after the Osteoporosis program was assumed to come into effect), the proportion of patients taking oral bisphosphonates only with a PDC of ≥ 80% was estimated to be 30.3%. Had the 2015 Osteoporosis program not taken place, the adherence rate was estimated to have declined by this time point to 27.8%. At the end of the study period (31 December 2019, 44 months after the Osteoporosis program was assumed to come into effect), the proportion of patients who were adherent to oral bisphosphonates was estimated to be 29.0%. Had the program not occurred, the modelled adherence rate was estimated to be 20.5%.

Table 13: **IMPACT OF THE 2015 OSTEOPOROSIS PROGRAM ON PROPORTION OF ADHERENT PATIENTS, ORAL BISPHOSPHONATES POPULATION**

Time point	Model	Estimated adherent population without the program (95% CI)	Estimated adherent population with the program (95% CI)	Absolute increase in adherence	Relative increase in adherence
31 May 2017	Trend	27.8% (27.1%, 28.5%)	30.3% (29.6%, 31.0%)	2.5%	8.9%
31 Dec 2019	Trend	20.5% (19.8%, 21.2%)	29.0% (28.3%, 29.8%)	8.5%	41.5%

Figure 4: **ESTIMATED IMPACT OF THE OSTEOPOROSIS PROGRAM ON PROPORTION OF ADHERENT PATIENTS, ORAL BISPHOSPHONATES POPULATION**



Note: The two dotted vertical lines indicate the time frame when the 2015 Osteoporosis program was delivered: from 1 October 2015 to 31 August 2016 (11 months)

1.7. Discussion

To assess the change in adherence to osteoporosis medicines following the 2015 Osteoporosis program, we conducted a retrospective cohort study, evaluating data reported over a timeframe of approximately 8 years. To inform the analysis, data were collected from the PBS pharmacy-claims-based database. A 10% sample of PBS data was used, with this reflecting use of medicines during this period for approximately 10% of the overall Australian population. The study population was selected by identifying patients who filled prescriptions for osteoporosis medicines during the study period. Given the necessity of good adherence for maintaining the clinical benefits of osteoporosis therapy, our findings provide evidence of the positive impact of the Osteoporosis program as well as timely information on real-world use of osteoporosis medicines in Australia.

Over the study period, one-third (33.7%) of patients in the all osteoporosis study population were treated with denosumab only; one-third (30.7%) were treated with oral bisphosphonates only; and just less than one-third (27.9%) switched osteoporosis medicines. The remaining patients were treated with either strontium, zoledronic acid, raloxifene or teriparatide only during the study period.

The 2015 Osteoporosis program was found to have had an impact on improving the rate of adherence with osteoporosis medicines compared to no intervention. Specifically, the clinical objective of the program, with respect to improving adherence by 10%, was exceeded, with an 11.3% relative increase in adherence within 12 months from the date the program was assumed to come into effect. There was a further increase in adherence by the end of the study period with an absolute increase of 16.6% and relative increase in adherence of 46.5%. The positive impact of the 2015 Osteoporosis program was more pronounced for the all osteoporosis population (which included patients who switched medications) and the patients who only took oral bisphosphonates during the entire study period.

It has been well-established in the international literature that improved adherence to osteoporosis treatment leads to reduced fracture risk [22,23] which results in reduced hospitalisations and mortality [24], and subsequently reduced costs to the health system [25]. Quantifying the improvement in adherence resulting from the impact of the 2015 Osteoporosis program into the number of fractures and hospitalisations avoided would give a much more relatable idea of program impact. Proper extrapolation analysis is complex and entails in-depth literature review and meta-analysis. In an ideal world with more funding, additional modelling in the form of an economic evaluation to quantify both the costs and the savings associated with this improved adherence would be desirable.

ITS analysis suggested that, for the all osteoporosis population, adherence increased and continued to increase with further time after the program. Given the strong downward trend for loss of adherence without the program, this was somewhat surprising. This suggests that it may take some time for program messages to be implemented in clinical practice. This is important to consider in the design and analysis of future programs aiming to investigate adherence with treatments for the prevention of chronic diseases. For example, it could be worthwhile to provide reinforcing messages for health professionals about adherence sometime after educational visiting has been completed.

Patients who took denosumab only during the entire study period had an aggregated adherence rate ranging between 64.2% and 77.3%. This was higher than that estimated for the all osteoporosis population. With higher baseline adherence, and therefore less room for improvement – and because denosumab is administered less frequently than all other treatments with the exception of zoledronic acid – we expected to see less of an increase in adherence for this sub-group. Despite this, it was concerning to find adherence to be this low for patients who were prescribed only denosumab during the study period. Given the drug is administered every 6 months, we would expect adherence to be higher for this sub-group of patients who were not switched to another osteoporotic medicine. General practices and patients need good systems in place to ensure timely return of patients to practices for 6-monthly injections.

According to the Healthy Bones Australia 2021 position statement,[19] there should be, “no treatment interruption with denosumab, as its effects are rapidly reversible. If, for whatever reason denosumab treatment cannot be continued, transition to an oral bisphosphonate for at least 12 months is recommended, commencing within 4 weeks of the missed dose”. The position statement also states, “if treatment is delayed, or ceased, bone loss may recur very quickly”, and, “if there is a good reason to stop denosumab (such as an adverse reaction) it is recommended to commence oral bisphosphonate therapy immediately to reduce the risk of a rapid decrease in BMD, and the resultant increased risk of vertebral fractures”.

Poor adherence in this sub-group of patients prescribed only denosumab suggests that some patients would have experienced a period of treatment discontinuation, placing them at increased risk of fracture.

Adherence rates for patients using oral bisphosphonates only was low. Modelling suggested that without the program, adherence rates would have fallen to 20.5% for patients who continued to receive a prescription for an oral bisphosphonate. It is important for patients prescribed osteoporosis medicines to continue to take their medicine as prescribed. The 2015 Osteoporosis program resulted in improved adherence among patients who continued to be prescribed oral bisphosphonates. It is also likely that the program prompted GPs to review their patients’ treatments more regularly. This may have resulted in GPs switching patients to an alternative treatment, better suited to the patient’s needs, more often.

Overall, adherence was sub-optimal for all osteoporosis medicine groups. The PDC values observed in the study were lower than those reported in other publications on anti-osteoporotic therapy. This is not surprising given a more conservative method was used to calculate the PDC (ie, assuming treatment break as non-adherence) and the duration of the study was considerably longer than that of other studies, which are mostly 1–2 years.[26,27] It is not possible to directly compare adherence

calculated in our study with that of other studies, due to the differences in methodologies and measures used by other researchers.

Within the Australian context, a 2004 retrospective analysis of dispensing data showed that only 57% of Australians with osteoporosis persisted with bisphosphonate treatment after 12 months.[28] The level of adherence to denosumab since its addition to the PBS in 2010 remains unknown.[8] Within the international context, a study conducted in the Czech Republic to measure adherence to denosumab in the treatment of osteoporosis found a high adherence rate. The majority of patients (93.8%) had a medication possession ratio (MPR) ≥ 80%.[27] However, the time frame of this study was only 2.5 years and the study population was limited to women with postmenopausal osteoporosis.

The results from this study will help inform the PBS Practice Review focused on medicines for osteoporosis that has been in planning during 2021-22.

Strengths and limitations

Strengths of this study included the following:

- The 10% PBS sample contains patient-level data. Patients within the 10% dataset cohort were broadly representative of the Australian population in terms of patient demographics, rates of disease, and prevalence rate of people receiving treatment. Within this study cohort of patients aged 45 years or older, the overall prevalence rate of people receiving osteoporosis treatment was 8.11%, with higher rate in women (12.53%) than in men (3.40%). The overall prevalence rate is somewhat lower compared with those from other studies in Australia. For example, using MedicineInsight data, Naik-Panvelkar et al. estimated the overall prevalence of osteoporosis in Australian general practice as 12.4%, with significantly more women (17.6%) than men (5.3%) having a recorded diagnosis.[8] Another study provided estimates based on rates of BMD measurement (men: 6%, women: 23%, Geelong Osteoporosis Study).[29] Reasons for the difference in estimates may include differences in study population selection (eg, age groups), definitions of osteoporosis, types of records accessed and/or methods of detecting/confirming osteoporosis.
- The study analysed treatment for all patients prescribed an osteoporosis medicine aged 45 years or older who had more than 12 months of follow-up data, including patients who started osteoporosis treatment prior to 1 December 2011 (the start of the study). The reasonably large sample size allowed us to conduct separate analyses for two medicine groups to confirm the findings of the primary analysis (the all osteoporosis study population).
- ITS was used as it is a robust statistical methodology for assessing impact with population-level intervention programs.

The study had several limitations:

- The 10% PBS data did not provide information on reasons for refill gaps. Therefore, a conservative approach was used to calculate the PDC, assuming that treatment breaks reflected non-adherence. Many studies in the literature considered a refill gap of 30 days or 60 days as permissible.[26] However, given that the majority of patients within the study were taking denosumab and osteoporosis medicines other than oral bisphosphonates and zoledronic acid, we considered our approach was reasonable.
- It was not possible to determine whether the patients in the 10% PBS sample accurately represented patients directly impacted by the program. To overcome this problem, in the future, we would recommend linking MedicineInsight and PBS data. This would provide a greater range of analysis methods, allowing measurement of changes in adherence more accurately using patient-level data.
- Finally, this was a retrospective observational study. A more robust study design would be a randomised controlled trial that measured patient adherence as an outcome. However,

implementing a randomised controlled trial at a large population level was not logistically or financially viable.

Assumptions underlying the results of this study:

- We assumed that the 10% PBS data sample that we received accurately represented the PBS data for the overall Australian population during the study period.
- We also assumed that patients who had a prescription filled took the medicine. We considered this assumption to be reasonable with respect to injectable medicines, but having a prescription filled may not necessarily have translated to use of medicines administered orally.

1.8. Conclusion

In conclusion, the study demonstrated that the 2015 Osteoporosis program improved the rate of adherence to osteoporosis medicines compared with no intervention. This positive impact was demonstrated for the all osteoporosis study population as well as patients taking denosumab only and oral bisphosphonates only during the entire study period. The program met its objective of increasing adherence to osteoporosis medicines by at least 10%.

Despite the positive impact of the 2015 Osteoporosis program on improving the rate of adherence to osteoporosis medicines, the observed adherence rate for the all osteoporosis study population was sub-optimal. Compared with patients taking oral bisphosphonates only, patients taking only denosumab had an overall higher observed adherence rate. This may be attributable to the convenient once-in-6-month dosing schedule and good tolerability of denosumab, but also to different characteristics of patients treated with this medicine compared with those treated with oral bisphosphonates. Despite this, given the considerable increase in fracture risk associated with discontinuation, strategies to enhance adherence to denosumab are still needed.

Poor adherence to osteoporosis medicines is a well-documented phenomenon described in the international literature. The factors leading to non-adherence are complex.[30] Factors affecting osteoporosis management include poor patient awareness of the potential impact of osteoporosis; concerns about side effects prior to starting treatment along with actual side effects once started; lack of perceived obvious benefits while on treatment; negative impressions of medicines from the media or friends/family; and cost.

Future programs should continue to address the importance of adherence to improve patients' clinical outcomes and quality of life, and to reduce unnecessary healthcare costs. A focused and tailored program designed to emphasise the importance of long-term adherence with denosumab (including a switch to bisphosphonates if treatment needs to be discontinued) may be warranted to further improve QUM.

APPENDIX 1. ATC AND PBS ITEM CODES FOR MEDICINES

The following ATC codes and medicine names were used to identify prescriptions of osteoporosis in the 10% PBS data.

Table 14: **OSTEOPOROSIS MEDICINES – ATC AND PBS ITEM CODES USED IN THIS ANALYSIS**

ITEM_CODE	GENERIC	ATC5
08102K	ALENDRONATE	M05BA04
08511Y	ALENDRONATE	M05BA04
09012H	ALENDRONATE + COLECALCIFEROL	M05BB03
09183H	ALENDRONATE + COLECALCIFEROL	M05BB03
09351E	ALENDRONATE + COLECALCIFEROL (&) CALCIUM CARBONATE	M05BB05
05457F	DENOSUMAB	M05BX04
08363E	RALOXIFENE HYDROCHLORIDE	G03XC01
08481J	RISEDRONATE	M05BA07
08621R	RISEDRONATE	M05BA07
08972F	RISEDRONATE	M05BA07
09391G	RISEDRONATE	M05BA07
08899J	RISEDRONATE (&) CALCIUM CARBONATE	M05BB02
09147K	RISEDRONATE (&) CALCIUM CARBONATE + COLECALCIFEROL	M05BB04
03036T	STRONTIUM RANELATE	M05BX03
09411H	TERIPARATIDE	H05AA02
12670W	TERIPARATIDE	H05AA02
09288W	ZOLEDRONIC ACID	M05BA08
10555M	ZOLEDRONIC ACID	M05BA08
12301K	ROMOSOZUMAB	M05BX06

Note: ROMOSOZUMAB was not considered in this analysis as this medicine was not listed on the PBS until 21 April 2021.

APPENDIX 2. TREATMENT DURATION OF THERAPY FOR OSTEOPOROSIS MEDICINES

Table 15: EXPECTED DURATION OF THERAPY FOR OSTEOPOROSIS MEDICINES

DRUG	EXPECTED DURATION OF THERAPY (DAYS)
ALENDRONATE (including combination products)	28
RISEDRONATE (including combination products)	28
RALOXIFENE	28
STRONTIUM	28
DENOSUMAB	180
ETIDRONATE DISODIUM (&) CALCIUM CARBONATE	90
ZOLEDRONIC ACID	365
TERIPARATIDE	28

Table 16: ROUTE AND FREQUENCY OF ADMINISTRATION OF OSTEOPOROSIS MEDICINES

GENERIC NAME	ROUTE AND FREQUENCY OF ADMINISTRATION
Alendronate and combinations (alendronate with colecalciferol; alendronate with colecalciferol and calcium carbonate)	Oral; daily or weekly
Denosumab	Subcutaneous injection; once every six months
Raloxifene	Oral; daily
Risedronate and combinations (risedronate and calcium carbonate; risedronate and calcium carbonate with colecalciferol)	Oral; daily, weekly or monthly
Strontium ranelate	Granules for oral suspension; daily at bedtime
Teriparatide (RBE)	Subcutaneous injection; daily. Max 18 months
Zoledronic acid	IV infusion; once per year

APPENDIX 3. INTERRUPTED TIME SERIES METHODOLOGY

Overview

Interrupted time series (ITS) analysis, also known as intervention modelling, is the gold standard approach for assessing impact with population-level intervention programs in public health.[10,31] ITS is a quantitative, statistical method in which multiple repeated observations are made at regular intervals before and after an intervention (the 'interruption' in the time series). Statistical analysis is performed to determine whether there is a change in the observations, or trend of observations, following an intervention.

ITS analysis of adherence to osteoporosis medicines provided the following key outputs:

1. A time series model is fitted to the monthly adherence measure (referred to as the 'actual' series).
2. The time series model forecasts what the series of the adherence measure would have been had the intervention(s) not taken place (referred to as the 'counterfactual series').

The two series are then compared ('counterfactual' less 'actual') to estimate the impact of the intervention(s).

Assumptions of ITS

- Past behaviour of the time series of the adherence measure is predictive of what would have happened if the intervention(s) did not occur.
- All model variables selected in the final model account for and drive any changes in the adherence measures as observed over the study period.
- Events identified for modelling need to have clear times of impact (typically the month of the event or start month if a continually impacting event). If an external event is identified during the intervention(s) then it is difficult to model this event separately and it may instead be captured in the intervention term.
- ITS modelling can only be conducted with a reasonable level of statistical power provided there are at least 24 months-worth of time points available. This is to ensure any changes in adherence trends before the intervention(s) can be appropriately observed and assessed.
- The validity of conclusions and inference from time series models relies on fulfilling theoretical assumptions fundamental in applying time series analysis. This includes, but is not limited to: residuals are distributed normally once autocorrelation is accounted for; residuals have no autocorrelation (ie, independence with one another or across time); and homoscedasticity of residuals across time (ie, equal variance). At each step of the model fitting process these critical time series modelling assumptions are checked to ensure the final models selected and reported fulfil these criteria.

Fitting an ITS model

Time series modelling for this report was generated using SAS software (SAS Enterprise Guide V 7.15, Cary NC USA, 2017). The first step in fitting a time series model is model selection, which identifies variables to test and include in analysis. Variables for testing, and specified for each model produced, are broadly categorised into: intervention terms; non-intervention terms; seasonal terms; and autocorrelation terms.

At each stage of model specification, the coefficient's estimate, standard error, p-value and correlation estimates are examined to ensure the inclusion of a coefficient to the model specification is warranted. Well-known model fitting criteria are checked to ensure the better fitting model(s) are identified: the Akaike Information Criterion (AIC); Schwarz's Bayesian Information Criterion (SBC); and the Standard Error estimate. These criteria offer guidance in deciding whether a candidate model offers a better fit over another model specification. These criteria do not provide a statistical test between models in the sense of accepting or rejecting a null hypothesis, nor indicate how good the model is in an absolute sense. Generally, models with smaller AICs, SBCs and standard error of estimates provide a better fit to the data.[21,32]

Intervention terms

ITS modelling provides the opportunity to build model terms that can explore the nature of the change in adherence measures due to the NPS MedicineWise intervention. ITS models these events as separate variables, and their statistical significance determines whether a change in the monthly measures of adherence can be explained by the intervention variables. The way in which either events change monthly measure of adherence may take one of, or a combination of, the following model intervention terms:

- Step or level change: a sudden and constant change in the adherence measure over time.
- Trend change: a sudden and either increasing or decreasing change in the adherence measure over time.

Models using different functional forms of the NPS MedicineWise intervention term were compared by using model fitting criteria discussed above.

Trend

In estimating the effect of the NPS MedicineWise model intervention term, it was important to have controlled for any pre-existing trend in the adherence measures.[32,33] This was achieved through an underlying trend term. The functional form of the trend may also take a curvilinear form over time (for example, a square root or quadratic function of trend) and this was explored during the iterative model building process.

Seasonal terms

Seasonal variation is a regular component of a time series and is defined as an event that occurs repetitively and predictably at the same time each year. For monthly time series, seasonal variation can be observed quarterly, semi-annually or annually.

Seasonality is modelled by dummy (binary) variables for each of the 11 months (excluding a reference dummy variable, typically taken as November). All dummy variables are retained in the final model provided the dummies are jointly significant (using a likelihood ratio test based on the Chi-square distribution). Note that the seasonal dummy variables are related to one another. Removing individual seasonal dummies alters this relationship and changes the interpretation, particularly what the reference dummy variable is measuring. Excluding some seasonal dummies based on individual significance is not recommended. The 11 dummy variables interreact and should be considered together.

Autocorrelation terms

A common feature of time series data is the presence of autocorrelation, where adjacent data points of the variable of interest are correlated in time. An autocorrelation structure estimates the inherent underlying pattern that exists between these time points. If autocorrelation is not accounted for in a time series model, the model will incorrectly calculate the estimates and standard errors of

coefficients. This can result in misleading conclusions for individual coefficients in the model produced. Where no autocorrelation structure is applied – a variable may have a significant p-value. However, this variable may not actually be significant once an autocorrelation structure is specified.

An autocorrelation structure involves the specification of autoregressive (AR) lagged terms denoted as '*p*', and/or moving average (MA) lagged terms denoted as '*q*' (or some combination of these two terms) to estimate the correlation between time points. Once the intervention, non-intervention and seasonal terms have been fitted to a time series, there are two steps involved in fitting AR and/or MA terms:

1. Identify the presence of autocorrelation using diagnostic methods (outlined below); and
2. Where it exists, incorporate autocorrelation terms into the model.[33]

Residual correlation diagnostics were outputted from the PROC ARIMA procedure in SAS. The autocorrelation function (ACF) plots and partial autocorrelation function (PACF) plots provided guidance in selecting the appropriate autocorrelation structure.

Final model selection

After the models were specified with AR and/or MA terms, additional tests and criteria were examined to ensure the model selected sustained the assumptions of time series analysis. Where competing explanatory models existed, the AIC for each model were compared to determine the best fitting model. Model fitting criteria and coefficient estimates were examined in the final model selection process. At any stage of this process, any of the steps described above can be applied iteratively until the pattern of dispensing behaviour is modelled appropriately.

In addition to providing visualisations of ACF and PACF plots and selecting AR and/or MA terms, SAS software output tests of the autocorrelations of the residuals to lags of 6, 12, 18 and 24 months. The chi-squared test statistics for the residual series tested the hypothesis that the residuals are uncorrelated (white noise) and therefore don't violate the assumptions of time series modelling. If an appropriate autocorrelation structure is specified, all tests from lags of 6 months to 24 months should display p-values larger than 0.05. Final selected models report autocorrelation checks on residuals.

Normality tests (Shapiro–Wilk) were used to assess the degree to which the normality assumption was upheld, in addition to visually inspecting the distribution and quantile–quantile plot of residuals output from SAS software. The distribution and quantile–quantile plot of residuals from the final models selected were visually inspected for any deviance from normality.

Residuals were plotted against time to check homoscedasticity to identify time periods where the model did not fit the data well. This was particularly important with respect to trend patterns estimated for time points immediately preceding the onset of the Osteoporosis program. If the estimated pre-existing trend was large, this would have the spurious effect of over-estimating the co-efficient for the NPS MedicineWise intervention terms.

REFERENCES

1. Easton K BJ, Naik-Panvelkar P, Raymond J. Formative Research: Osteoporosis. Sydney: NPS MedicineWise, 2014.
2. MedicineWise N. NPS Program Evaluation. Preventing Fractures – Where to start with Osteoporosis: Evaluation Report. Sydney: NPS MedicineWise, 2016
3. Gupta A, March L. Treating osteoporosis. Aust Prescr 2016;39:40-6. https://www.ncbi.nlm.nih.gov/pubmed/27340321
4. Ross S, Samuels E, Gairy K, et al. A meta-analysis of osteoporotic fracture risk with medication nonadherence. Value in Health 2011;14:571-81. https://pubmed.ncbi.nlm.nih.gov/21669382/
5. Australian Institute of Health and Welfare. Use of antiresorptive agents for osteoporosis management. Canberra: AIHW, 2011. https://www.aihw.gov.au/getmedia/e4038a33-2c7f-431b-b4db-8468349eb364/11354.pdf.aspx (accessed 22 February).
6. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. Bone 2017;105 11-7. https://pubmed.ncbi.nlm.nih.gov/28789921/
7. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97. https://pubmed.ncbi.nlm.nih.gov/16079372/
8. Naik-Panvelkar P, Norman S, Elgebaly Z, et al. Osteoporosis management in Australian general practice: an analysis of current osteoporosis treatment patterns and gaps in practice. BMC Fam Pract 2020;21:32. https://www.ncbi.nlm.nih.gov/pubmed/32050909
9. Penning-van Beest FJ, Erkens JA, Olson M, et al. Loss of treatment benefit due to low compliance with bisphosphonate therapy. Osteoporos Int 2008;19:511-7. https://www.ncbi.nlm.nih.gov/pubmed/17874028
10. Hudson J, Fielding S, Ramsay CR. Methodology and reporting characteristics of studies using interrupted time series design in healthcare. BMC Med Res Methodol 2019;19:1-7. https://pubmed.ncbi.nlm.nih.gov/31272382/
11. NPS MedicineWise. MEDICINEINSIGHT Feasibility study Osteoporosis. Sydney: NPS MedicineWise, 2018
12. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health 2008;11:44-7. https://www.ncbi.nlm.nih.gov/pubmed/18237359
13. Bijlsma MJ, Janssen F, Hak E. Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method. Pharmacoepidemiol Drug Saf 2016;25:325-32. https://www.ncbi.nlm.nih.gov/pubmed/26687394
14. Seeman E, Compston J, Adachi J, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. Osteoporos Int 2007;18:711-9. https://www.ncbi.nlm.nih.gov/pubmed/17245547
15. Kothawala P, Badamgarav E, Ryu S, et al. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. Mayo Clin Proc 2007;82:1493-501. https://www.ncbi.nlm.nih.gov/pubmed/18053457
16. Langdahl BL. Management of endocrine disease: Treatment breaks in long-term management of osteoporosis. Eur J Endocrinol 2019;180:R29-R35. https://www.ncbi.nlm.nih.gov/pubmed/30444721
17. Black DM, Bauer DC, Schwartz AV, et al. Continuing bisphosphonate treatment for osteoporosis--for whom and for how long? N Engl J Med 2012;366:2051-3. https://www.ncbi.nlm.nih.gov/pubmed/22571169
18. Elliott J and Naik-Panvelkar P. GP osteoporosis treatment pathways and perceptions of patient adherence to osteoporosis treatment. Sydney: NPS MedicineWise, 2018
19. Ebeling PR, Seeman E, Center J, et al. Position Statement on the Management of Osteoporosis. Healthy Bones Australia 2020.
20. RACGP. Osteoporosis risk assessment, diagnosis and management. Recommendations restricted to postmenopausal women and men aged >50 years, 2017

21. Enders W. Applied Econometric Time Series. Wiley series in probability and mathematical statistics. New York: Wiley, 1995.
22. Siris ES, Harris ST, Rosen CJ, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22. https://www.ncbi.nlm.nih.gov/pubmed/16901023
23. Weycker D, Lamerato L, Schooley S, et al. Adherence with bisphosphonate therapy and change in bone mineral density among women with osteoporosis or osteopenia in clinical practice. Osteoporos Int 2013;24:1483-9. https://www.ncbi.nlm.nih.gov/pubmed/22903292
24. Cooper C, Atkinson EJ, Jacobsen SJ, et al. Population-based study of survival after osteoporotic fractures. Am J Epidemiol 1993;137:1001-5. https://www.ncbi.nlm.nih.gov/pubmed/8317445
25. Ebeling PR. The burden of brittle bones: Epidemiology, costs and burden of osteoporosis in Australia. Sydney: International Osteoporosis Foundation and Osteoporosis Australia, 2007.
26. Netelenbos JC, Geusens PP, Ypma G, et al. Adherence and profile of non-persistence in patients treated for osteoporosis: a large-scale, long-term retrospective study in The Netherlands. Osteoporos Int 2011;22:1537-46. https://www.ncbi.nlm.nih.gov/pubmed/20838773
27. Fuksa L, Vytrisalova M. Adherence to denosumab in the treatment of osteoporosis and its utilization in the Czech Republic. Curr Med Res Opin 2015;31:1645-53. https://www.ncbi.nlm.nih.gov/pubmed/26121231
28. Sambrook P. Compliance with treatment in osteoporosis patients--an ongoing problem. Aust Fam Physician 2006;35:135-7. https://www.ncbi.nlm.nih.gov/pubmed/16525527
29. Henry MJ, Pasco JA, Nicholson GC, et al. Prevalence of osteoporosis in Australian men and women: Geelong Osteoporosis Study. The Medical Journal of Australia 2011;195:321-2.
30. Lindsay BR, Olufade T, Bauer J, et al. Patient-reported barriers to osteoporosis therapy. Arch Osteoporos 2016;11-19. https://www.ncbi.nlm.nih.gov/pubmed/27129487
31. Hudson J, Fielding S, Ramsay CR. Methodology and reporting characteristics of studies using interrupted time series design in healthcare. BMC Med Res Methodol 2019;19:137. https://pubmed.ncbi.nlm.nih.gov/31272382/
32. Wagner AK, Soumerai SB, Zhang F, et al. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002;27:299-309. https://www.ncbi.nlm.nih.gov/pubmed/12174032
33. Koop G. QR. Analysis of economic data. England: Wiley Chichester, 2000.