Appendix A. Standardization of Dosage of Bisphosphonates to Equivalent Alendronate Daily Dose

The cumulative dose of oral and IV bisphosphonate treatment received during the 12-month PMO baseline period and updated during the 12-month PMO exposure cohort baseline period will be calculated through standardization of dosage of various bisphosphonates to equivalent alendronate daily dose. Table 10 shows the algorithm for computing alendronate-equivalent daily dose for other oral and IV bisphosphonates. Using IV bisphosphoante as an example, to compute cumulative dosage of IV bisphosphonates during the baseline, one first computes "days supplied" for prescription claims for IV ibandronate or zoledronic acid. Days supplied is specified as the number of days from the claim date through the next anticipated administration date. Each IV bisphosphonate dose is then standardized to daily alendronate dose equivalents to harmonize different dosing frequencies among the various products, as follows:

1. For IV ibandronate 3-mg/3-month supply, the standardized days supplied is specified as 90 days, and the alendronate equivalent daily dose is 10 mg/day.
2. For IV zoledronic acid 5 mg/365 days supplied, the alendronate equivalent daily dose is 10 mg/day.

For example, a beneficiary with 2 claims for IV ibandronate would have a cumulative alendronate equivalent dose of 10 mg/day $\times$ 180 days = 1800 mg. If exposure began before the start of the baseline period and continued into the baseline period, only the exposed days in the baseline period are included in the calculation.

Table A-1. Algorithm for Computing Alendronate-equivalent Daily Dose for Oral and Intravenous BP

Drug	Dose/Strength	Monthly Dose (30)	Usual Dosing Interval	Duration of Exposure	Alendronate Equivalent Daily Dose
Alendronate	5 mg/day	150 mg	30	30	5 mg
	10 mg/day	300 mg	30	30	10 mg
	35 mg/wk	150 mg	28	28	5 mg
	70 mg/wk	300 mg	28	28	10 mg
Risedronate	5 mg/day	150 mg	30	30	10 mg
	35 mg/wk	150 mg	28	28	10 mg
	75 mg *2d/month	150 mg	28	28	10 mg
	150 mg/month	150 mg	30	30	10 mg
Oral Ibandronate	2.5 mg/day	75 mg	30	30	5 mg
	150 mg/month	150 mg	30	30	10 mg
IV Ibandronate	3 mg/84 days	N/A	90	90	10 mg
IV Zoledronic acid (Reclast)	5 mg/365 days	N/A	365	365	10 mg
	Assumed that 4 mg Zometa has equal effects on OP as 4 mg Reclast, we calculated the following BP agents				
IV Zoledronic acid (Zometa)	4 mg / month	4 mg	30	365	8 mg

	As 5 mg Reclast daily dose is equivalent to 10 mg alendronate, the 4 mg Zometa daily dose equals to 8 mg alendronate. Therefore, if someone received 3 dosages in 3 consecutive months, we will calculate alendronate equivalent daily dose as 8 mg in the first month, 16 mg in the second month and 24 mg in the third month.				
Pamidronate (Aredia)	90 mg/ month	90 mg	90*	90	8 mg
Oral Etidronic acid	400 mg/day	N/A	90†	90†	10 mg
IV Etidronic acid	1500 mg/course of 7 days	N/A	14‡	14‡	8 mg
Oral Clodronic acid	1600 mg/day	48000 mg	30	30	10 mg
IV Clodronic acid	1500 mg/course	N/A	90§	90§	10 mg
Ex_1: A 67 yo female beneficiary received Zoledronic Acid 5mg on April 1, 2009. She enters follow-up on May 26, 2010. Her 12-month baseline period is 05/26/09 – 05/25/10. Her daily ALN equivalent dose is 3650 mg on April 1, 2009 and is 0 mg thereafter. She is classified as having no exposure to BP (0 days exposed and 0 dose). Ex_2: A 71 yo female beneficiary received Alendronate 5 mg on October 1, 2010. She filled this prescription and took through May 31st of the following year. On June 1, 2011 her doctor prescribed her Risedronate 5 mg which she has continued to take daily. Upon entering the cohort on October 1, 2011 she has received a cumulative dose of 2400 mg (ALN equivalent dose) during the baseline period. This is calculated by summing [5 (mg) x number of days exposed] + [10 (mg) x number of days exposed].					

*This is the usual dosing interval for OP treatment.

† Treatment for the indication of PMO is given on a cyclic basis: 400 mg/day for 14 days followed by the equivalent of 500 mg of elemental calcium for 76 days.

‡ Treatment for the indication of hypocalcemia of malignancy: 1500 mg/course for 3-7 days followed by at least 7 day interval between courses.

§ The suggested dosing schedule for the treatment of OP: 1500 mg/course for 1-5 days every 3-month.

Appendix B. List of covariates

Variable	Time-fixed	Time-varying	Chronic condition
Demographic Factors			
Age Groups (years)		√	
Geographic Region (data system-specific)	√		
Length of enrollment in the data system	√		
Calendar Year	√		
Diseases			
Diabetes		√	√
Type I diabetes		√	√
Type II diabetes		√	√
End stage renal disease		√	√
HIV/AIDS		√	√
Liver cirrhosis		√	√
Cystic fibrosis		√	√
Chronic obstructive pulmonary disease		√	√
Chronic lung disease		√	√
Autoimmune diseases			
Lupus		√	√
Multiple sclerosis		√	√
Rheumatoid arthritis		√	√

Ankylosing spondylitis		√	√
Crohn's disease		√	√
Inflammatory bowel disease		√	√
Psoriasis		√	√
Rheumatic fever		√	√
Overweight/obesity		√	√
Serious infection		√	
Serious neutropenia		√	
Decubitus ulcer		√	
Fragility Fracture		√	
Charlson Comorbidity Index		√	
Medications			
Other OP medication(s)		√	
Corticosteroid (oral or injectable)		√	
Anti-diabetics		√	
Immunosuppressant drugs		√	
Healthcare Utilizations			
Number of Office/outpatient Visits to physicians	√		
Number of Different types of drugs dispensed (based on medication class or indication?)	√		
Number of Emergency room	√		

visits			
Days of hospitalization	√		
Others			
Malnutrition		√	

Appendix C. Steps to calculate the stabilized weight for MSM

(1) The numerator and denominator of the stabilized weight of treatment for person i at time t, denoted $SWi(t)_{treatment}$ were estimated using two pooled multinomial logistic regression models, with received OP medication as the dependent variable. Independent variables for the numerator model included time-fixed covariates and the denominator model included both time-fixed and time-varying covariates. Time since start of follow-up was accounted for in both numerator and denominator models by modeling the time dependent intercepts smoothly using natural cubic splines.

(2) The numerator and denominator of the stabilized weight of censoring for person i at time t, denoted, $SWi(t)_{censoring}$ were estimated using two pooled logistic regression models estimating the predicted probability of remaining uncensored using the same method as the estimation for $SWi(t)_{treatment}$.

(3) A new dataset that contained, for each visit the original variables plus the 4 predicted probabilities of treatment and censoring estimated from steps (1) and (2) were generated.

(4) The numerator and denominator of the treatment weight were calculated as the product of predicted probabilities of receiving the treatment patients did indeed receive at each occasion up to time t, $SWi(t)_{treatment}$ obtained in step (1). The numerator and denominator of the censoring weight were likewise calculated by multiplying the predicted probability of remaining uncensored up to time t, $SWi(t)_{censoring}$. A combined weight was obtained by the product of treatment and censoring weights at each time t for each person i remaining at risk for study outcomes.

Appendix D. The polytomous logistic regression models used to estimate treatment weights

Table D-1 Model for the denominator of stabilized weight of treatment for the analysis of serious infection (untreated is the reference group)

	BP Treated	Other OP Treated
Demographic Factors	**OR (95% CI)**	**OR (95% CI)**
Demographic factors		
Age in years	.981 (.968-.995)	.984 (.966-1.00)
Geographical Region		
Northeast	.915 (.857-.978)	1.09 (1.01-1.17)
Midwest	.879 (.800-.965)	1.10 (1.05-1.17)
West	1.05 (.991-1.10)	1.08 (.997-1.16)
South	1.0	1.0
Length of Enrollment in data system before the PMO index date		
>12 - 24 months	1.02 (.960-1.08)	.968 (.890-1.05)
>24 - 60 months	1.0	1.0
Length of Enrollment after index date		
Days of Follow up(cubic spline)	1.06 (1.03-1.09)	1.06 (1.03-1.10)
Days of Follow up(cubic spline, Knot1)	.860 (.815-.908)	.896 (.834-.962)
Days of Follow up(cubic spline, Knot2)	1.08 (1.00-1.16)	.945 (.853-1.05)
Days of Follow up(cubic spline, Knot3)	1.57 (1.45-1.69)	1.89 (1.70-2.10)
Calendar year of the PMO index date		
2006	1.23 (1.15-1.30)	.961 (.876-1.05)
2007	1.33 (1.23-1.45)	.776 (.725-.831)
2008	1.05 (.990-1.12)	.679 (.615-.749)
2009	1.10 (1.01-1.20)	.687 (.642-.735)
2010	.980 (.918-1.05)	.650 (.591-.715)
2004 & 2005	1.0	1.0
Comorbidities		
Diabetes		
Diabetes (Type I)	.865 (.801-.935)	.868 (.779-.968)
Diabetes (Type II)	.847 (.795-.901)	.840 (.770-.917)
ESRD	.849 (.784-.919)	1.02 (.919-1.13)
HIV/AIDS	1.42 (1.08-1.87)	1.07 (.728-1.58)
Liver Cirrhosis	.909 (.784-1.06)	1.07 (.882-1.29)

	BP Treated	Other OP Treated
Demographic Factors	**OR (95% CI)**	**OR (95% CI)**
Cystic Fibrosis	1.26 (.853-1.85)	1.60 (1.00-2.54)
Chronic Obstructive Pulmonary Disease	.917 (.861-.978)	.917 (.841-1.00)
Autoimmune diseases		
Lupus	1.01 (.895-1.14)	.994 (.844-1.17)
Multiple Sclerosis	.986 (.870-1.12)	.927 (.779-1.10)
Rheumatoid Arthritis	1.04 (.961-1.13)	.912 (.814-1.02)
Ankylosing Spondylitis	.987 (.785-1.24)	1.07 (.784-1.45)
Crohns	.917 (.779-1.08)	.957 (.772-1.19)
Inflammatory Bowel Disease	1.00 (.875-1.15)	1.08 (.903-1.30)
Psoriasis	.959 (.858-1.07)	.856 (.726-1.01)
Rheumatic Fever	.942 (.655-1.35)	.596 (.326-1.09)
Overweight/Obesity	.854 (.788-.926)	.835 (.744-.939)
Serious Infection	.906 (.845-.971)	.920 (.838-1.01)
Serious Neutropenia	1.04 (.875-1.24)	1.14 (.901-1.44)
Decubitus Ulcer	.830 (.707-.974)	.998 (.817-1.22)
Fragility Fracture	.327 (.307-.348)	.426 (.392-.463)
Charlson Comorbidity Index Score (categorized)		
0	.933 (.878-.991)	1.02 (.964-1.08)
1	.932 (.858-1.01)	.973 (.899-1.05)
> 1	1.0	1.0
Medications		
Corticosteroids	1.10 (.995-1.21)	.966 (.844-1.11)
Anti-Diabetic Medications	1.10 (1.03-1.17)	1.01 (.919-1.10)
Immunosuppressants	1.05 (1.00-1.10)	1.04 (.976-1.11)
Healthcare Utilization		
Number of Office/outpatient Visits to other physicians	.974 (.956-.993)	.978 (.953-1.00)
Types of Different drugs dispensed	1.07 (1.04-1.09)	1.08 (1.05-1.11)
Number of intensive care and critical care services use	.794 (.758-.832)	.847 (.797-.901)
Days of hospitalization	.996 (.972-1.02)	1.00 (.973-1.03)
Others		
Malnutrition	1.01 (.880-1.16)	1.21 (1.02-1.43)

Table D-2 Model for the denominator of stabilized weight of treatment for the analysis of general infection (untreated is the reference group)

	BP Treated	Other OP Treated
Demographic Factors	**OR (95% CI)**	**OR (95% CI)**
Demographic factors		
Age in years	.981 (.967-.995)	.983 (.964-1.00)
Geographical Region		
Northeast	.909 (.849-.975)	1.10 (1.02-1.19)
Midwest	.882 (.800-.972)	1.10 (1.04-1.17)
West	1.06 (.998-1.12)	1.06 (.978-1.15)
South	1.0	1.0
Length of Enrollment in data system before the PMO index date		
>12 - 24 months	1.03 (.971-1.10)	.985 (.903-1.07)
>24 - 60 months	1.0	1.0
Length of Enrollment after index date		
Days of Follow up(cubic spline)	1.06 (1.03-1.09)	1.07 (1.03-1.11)
Days of Follow up(cubic spline, Knot1)	.863 (.815-.914)	.907 (.840-.979)
Days of Follow up(cubic spline, Knot2)	1.04 (.965-1.13)	.892 (.800-.996)
Days of Follow up(cubic spline, Knot3)	1.68 (1.54-1.83)	2.09 (1.87-2.34)
Calendar year of the PMO index date		
2006	1.22 (1.15-1.31)	.977 (.887-1.08)
2007	1.33 (1.22-1.45)	.778 (.724-.835)
2008	1.06 (.994-1.14)	.680 (.615-.753)
2009	1.11 (1.01-1.22)	.671 (.626-.720)
2010	.995 (.928-1.07)	.632 (.573-.697)
2004 & 2005	1.0	1.0
Comorbidities		
Diabetes		
Diabetes (Type I)	.866 (.797-.941)	.852 (.759-.957)
Diabetes (Type II)	.851 (.796-.910)	.839 (.765-.920)
ESRD	.843 (.774-.918)	1.02 (.914-1.14)
HIV/AIDS	1.51 (1.14-2.01)	1.11 (.748-1.65)
Liver Cirrhosis	.898 (.766-1.05)	1.07 (.880-1.31)
Cystic Fibrosis	1.10 (.734-1.64)	1.55 (.972-2.47)
Chronic Obstructive Pulmonary Disease	.915 (.854-.981)	.897 (.817-.985)
Autoimmune diseases		
Lupus	1.03 (.905-1.18)	1.03 (.867-1.23)
Multiple Sclerosis	.987 (.863-1.13)	.929 (.773-1.12)

	BP Treated	Other OP Treated
Demographic Factors	**OR (95% CI)**	**OR (95% CI)**
Rheumatoid Arthritis	1.03 (.949-1.13)	.867 (.767-.979)
Ankylosing Spondylitis	1.01 (.786-1.29)	1.13 (.818-1.57)
Crohns	.934 (.783-1.11)	.897 (.712-1.13)
Inflammatory Bowel Disease	.998 (.860-1.16)	1.12 (.920-1.35)
Psoriasis	.964 (.853-1.09)	.849 (.711-1.01)
Rheumatic Fever	.851 (.577-1.26)	.436 (.214-.890)
Overweight/Obesity	.853 (.782-.932)	.833 (.735-.944)
General Infection	.849 (.803-.897)	.868 (.807-.934)
Serious Neutropenia	1.04 (.858-1.25)	1.15 (.897-1.48)
Decubitus Ulcer	.816 (.689-.966)	1.01 (.823-1.24)
Fragility Fracture	.294 (.275-.313)	.386 (.354-.421)
Charlson Comorbidity Index Score (categorized)		
0	.948 (.888-1.01)	1.03 (.965-1.09)
1	.938 (.859-1.02)	.982 (.903-1.07)
> 1	1.0	1.0
Medications		
Corticosteroids	1.08 (.971-1.20)	.949 (.821-1.10)
Anti-Diabetic Medications	1.09 (1.02-1.17)	1.00 (.911-1.10)
Immunosuppressants	1.05 (.995-1.10)	1.03 (.965-1.11)
Healthcare Utilization		
Number of Office/outpatient Visits to other physicians	.968 (.949-.988)	.972 (.946-.999)
Types of Different drugs dispensed	1.08 (1.05-1.10)	1.09 (1.06-1.13)
Number of intensive care and critical care services use	.789 (.751-.829)	.837 (.785-.893)
Days of hospitalization	.994 (.969-1.02)	1.00 (.971-1.03)
Others		
Malnutrition	1.00 (.868-1.16)	1.17 (.977-1.40)