National Essential Drug List
Tertiary/Quaternary Medication Review Process

TITLE: Intravenous bisphosphonates for the secondary prevention of osteoporosis-associated fractures
Date: March 2024

Key findings

- Oral bisphosphonates are approved at an Adult Hospital Level for secondary prevention of osteoporosis-associated fractures.
- Motivation was received for consideration of intravenous (IV) bisphosphonates for the secondary prevention of osteoporosis factures in patients unable to tolerate oral bisphosphonates or where oral bisphosphonates are contraindicated.
- Oral and IV bisphosphonates have been shown to be non-inferior terms of antifracture efficacy.[1,5,7]
- There may be an increased risk of osteonecrosis of the jaw with use of IV bisphosphonates as compared to oral bisphosphonates, however this has not been adequately quantified, and the risk is lower than that seen in the oncology setting where higher doses are used.[6]
- Oral bisphosphonates are still more affordable than IV bisphosphonates, however at current pricing, the annual use of IV zoledronate will only account for an approximate extra R20 per patient per year on IV bisphosphonates.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

It is recommended that IV bisphosphonates be considered for the secondary prevention of osteoporosis-associated fractures in patients unable to tolerate oral bisphosphonates, or in patients where oral bisphosphonates are contraindicated. Currently the most affordable IV bisphosphonate option is zoledronate, largely due to its annual dosing, as compared to ibandronate that requires 3 monthly dosing.

Rationale: In certain patient groups, the oral use of bisphosphonates is not possible due to lack of ability to stay upright after oral administration, and certain medical conditions. IV bisphosphonates are comparable to oral bisphosphonates in terms of fracture prevention. IV bisphosphonates may carry a higher risk for osteonecrosis of the jaw (ONJ) and thus patients should be appropriately monitored.

Level of Evidence:

(Refer to appendix 1 for the evidence to decision framework)

BACKGROUND

Bisphosphonates are potent inhibitors of osteoclastic bone resorption and have been used in clinical practice for the treatment of metabolic bone diseases. In South Africa, oral alendronate, oral risedronate, intravenous (IV) ibandronate and IV zoledronate are registered for the treatment of osteoporosis.[1] Bisphosphonates have been shown to prevent 50-70% of vertebral fractures and 40-50% of hip fractures in clinical trials.[6]

The Adult Hospital Level Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) currently recommend the use of oral bisphosphonates for the secondary prevention of osteoporotic fracture in severe osteoporosis (patients who have a T-score of -2.5 plus an osteoporotic fracture); and for glucocorticoid-induced osteoporosis (patient on long-term, >3 months, corticosteroids at doses ≥ 5 mg/day).[2]

Although, the Adult Expert Review Committee review conducted in 2017 recommended bisphosphonate therapy for the secondary prevention of fragility fracture, it concluded that specific bisphosphonate was found to be superior over the other in terms of this outcome (this included analysis of both oral and IV bisphosphonates). The review also found that IV bisphosphonates were more likely to predispose patients to osteonecrosis of the jaw.[3]

Currently no intravenous bisphosphonates are approved for osteoporosis on the EML. Since anecdotally, some patients are unable to tolerate oral bisphosphonates, or oral bisphosphonates are contraindicated*; motivation was received to consider an IV bisphosphonate in this indication.

No evidence was identified for the particular population of interest (those who are unable to tolerate oral bisphosphonates or those where oral bisphosphonates may be contraindicated), and thus the population was simplified. Thus, this review seeks to determine non-inferiority between oral and IV bisphosphonates; and investigate the implications and impact of using IV bisphosphonates in patients who are unable to take oral, including that of cost.

Oral bisphosphonates should be avoided in patients who are at a higher risk of these gastrointestinal adverse effects, including those who are not able to sit upright for at least 30 minutes after taking the bisphosphonate, and patients with oesophageal disorders such as achalasia, oesophageal stricture, Barrett's oesophagus, and oesophageal varices as well as patients who have undergone Roux-en-Y gastric bypass.[4]

Purpose/Objective i.e. PICO

-P *(patient/population):* Patients with osteoporosis (i.e. T-score ≤-2.5) plus an osteoporotic fracture (secondary prevention).

-I *(intervention):* intravenous bisphosphonates

-C *(comparator):* oral bisphosphonates

-O *(outcome)**:*

- Development of clinical fractures
- Hospitalisation
- Safety

-S *(study type):* Systematic review and meta-analysis; randomised controlled trials.

*** bone mineral density not included as a hard clinical outcome in secondary osteoporosis.*

Methods

A rapid literature search was conducted in PubMed in February 2023 (See Appendix 2). Abstract and title screening, as well as full text review, was undertaken. A Cochrane Risk of Bias 1 assessment was conducted independently by two reviewers and conflicts resolved by discussion (JR and KM).

Results

The search yielded 37 meta-analyses and systematic reviews; and 57 randomised controlled trials (RCTs). Of these, one systematic review (for adverse effect of osteonecrosis of the jaw) and 1 post-hoc analysis of an RCT was identified for inclusion. Additionally, the systematic review and economic evaluation utilised it the Adult ERC Review was considered (however this was not specific to osteoporosis, and rather included all high-risk groups without the comparison of IV to oral). See appendix 3: Excluded studies.

Table 1: Summary of included studies

Citation	Study design	Population (n)	Treatment	Main findings *(details below in efficacy discussion)*
Ito et.al. 2017 (MOVER)[5]	Post-hoc analysis of a randomised, double-blind, active drug controlled trial (MOVER).	Subgroup n = 1134 Patients with prevalent vertebral fractures (1 or ≥2, and ≥ 3) at screening and femoral neck bone mineral density T scores ≥ -2.5 or <2.5, and < - 3.0 at baseline0	Ibandronate IV 0.5mg/month (376) OR Ibandronate IV1mg/month (382) OR Risedronate oral 2.5mg (376)	Overall incidence of vertebral fractures over 3 years was 16.1% (95% CI 12.2 – 19.9%) for IV ibandronate 1 mg; 19.9% (95% CI 15.6 – 24.1%) with ibandronate 0.5 mg; and 17.6% (95%CI 13.6 to 21.6%) for risedronate.

Carmona et.al. 2013[6]	Systematic Review of meta-analyses, systematic reviews and clinical trials	18 articles: 8 RCTs, 7 double-blind RCTs, 1 open clinical trial, 2 meta-analyses. Majority of population = middle-aged women with osteoporosis	Bisphosphonate exposure (alendronate, IV and oral ibandronate, risedronate, IV zoledronate)	• Majority of studies included found no cases of osteonecrosis of the jaw (ONJ). • One RCT found 2 cases: one in zoledronate group and one in placebo group. • One systematic review identified 368 cases of ONJ (94% with IV bisphosphonates, and 6% with oral bisphosphonates (estimated incidence with IV bisphosphonates 3-10%). • Less than 25% of ONJ cases occurred spontaneously, with factors associated with its occurrence being mainly dental procedures and to a lesser extent defective dentures, trauma, bone exostosis and drug therapy (corticosteroids).
Davis et.al. 2016[7]	Systematic Review and Economic evaluation	46 RCTs (27 studies providing data for fracture NMA	Alendronate; risedronate; ibandronate; zoledronate	• Network meta-analysis showed all treatments to be associated with beneficial effects on outcomes including fracture relative to placebo. Osteonecrosis more commonly reported in participants with malignancy receiving zoledronic acid, and usually associated with other factors.

The study was assessed as unclear risk of bias due to potential bias in outcomes data as the data for the subgroup analyses were drawn from the per protocol population of the MOVER study group.[8] It was also not clear due to the different formulations if a double dummy was utilised - See table 3.

Table 3: Risk of bias

	Ito et.al, 2017
Random Sequence Generation (selection bias)	**Low**
Allocation Concealment (selection bias)	**Low**
Blinding of participants and personnel (performance bias)	**unclear**
Blinding of outcome assessment (detection bias)	**Low**
Incomplete Outcome Data (attrition bias)	**unclear**
Selective Reporting (reporting bias)	**Low**
Other Bias	**Low**
OVERALL	**Unclear**

Outcomes

Efficacy

Development of Fractures

Ito et.al 2017[5]

- Overall incidence of vertebral fractures over 3 years was 16.1% (95% CI 12.2 – 19.9%, n=382) for IV ibandronate 1 mg; 19.9% (95% CI 15.6 – 24.1%, n=376) with ibandronate 0.5 mg; and 17.6% (95%CI 13.6 to 21.6%, n=376) for risedronate.

- Incidence vertebral fractures after 3 years in patient subgroups with baseline femoral neck BMD T Scores <-2.5, <-3

  The vertebral fracture incidence was consistently lower, but not significantly so, with monthly IV ibandronate 1mg than with the other treatments, regardless of the baseline FN BMD T score.

	T-score < -2.5 (95% CI)	T-score < -3 (95% CI)
IV ibandronate 1 mg	16.4% (10.1 to 22.7%)	21.4% (11.7 to 31.0%)
IV ibandronate 0.5 mg	24.6% (18 to 31.2%)	28.4% (18 to 38.8%)
Oral risedronate 2.5 mg	19.1% (13.2 to 25%)	22.2% (13.6 to 30.8%)

- Incidence of vertebral fractures after 3 years in patients with 1, ≥2 and ≥3 vertebral fractures

	1 prevalent vertebral fracture (95% CI)	≥ 2 prevalent vertebral fractures (95% CI)	≥ 3 prevalent vertebral fractures (95% CI)
IV ibandronate 1 mg	11.2% (6.3 to 13.1%)	20.4% (14.6 to 26.3%)	25.2% (15.8 to 34.6%)
IV ibandronate 0.5 mg	15.1% (9.7 to 20.4%)	24.7% (18.2 to 31.3%)	28.5% (18.5 to 38.4%)
Oral risedronate 2.5 mg	12.6% (7.5 to 17.7%)	22.1% (16 to 28.2%)	31.3% (21.8 to 40.8%)

- Incidence non-vertebral fractures after 3 years in patient subgroups with baseline T Scores ≥ -2.5, <-2.5, <-3

  Incidence of non-vertebral fractures in the sub-groups of patients with FN BMD T Score < -2.5 and <-3 after 36 months was reported to be not significantly different [(HR IV ibandronate vs oral risedronate 0.87 (CI 0.39 – 1.94) and 0.74 (CI 0.27 -2.03) respectively].

	T-score < -2.5	T-score < -3
IV ibandronate 1 mg	7.6%	8.5%
IV ibandronate 0.5 mg	10.8%	12.3%
Oral risedronate 2.5 mg	9.4%	12.4%

- Overall incidence of non - vertebral fractures over 3 years in patients with 1, ≥2 and ≥3 prevalent non-vertebral fractures

	1 prevalent non-vertebral fracture	≥ 2 prevalent non-vertebral fractures	≥ 3 prevalent non-vertebral fractures
IV ibandronate 1 mg	6.8%	7.6%	7.4%
IV ibandronate 0.5 mg	10.2%	7.8%	8.5%
Oral risedronate 2.5 mg	7.2%	9.5%	10.1%

Davis 2016[7]

Forty-six RCTs were included in the effectiveness systematic review (27 RCTs providing data for fracture network meta-analysis (NMA) and 35 RCTs providing data for femoral neck BMD NMA. All the bisphosphonates had beneficial effects on fractures as compared to placebo; and vertebral fractures and percentage change in BMD were statistically significant. There was no evidence of difference in effect on fractures between bisphosphonates (oral and IV; and various bisphosphonates).

Adverse events

The Adult Review identified the possible higher risk of osteonecrosis of the jaw (ONJ) with use of IV bisphosphonates particularly zoledronate.

The risk of osteonecrosis of the jaw has been linked to cancer patients receiving IV bisphosphonate therapy at much higher doses (and multiple other risk factors) than in the osteoporosis setting. Carmona et.al. reported that there is "insufficient evidence to affirm that IV or oral bisphosphonates used exclusively for the treatment of osteoporosis lead to a significant risk of ONJ (evidence level 2a, grade B recommendations)".[6] In Davis et.al. four placebo-controlled RCTs evaluated zoledronic acid, one compared zoledronic acid with risedronic acid and one compared zoledronic acid with alendronic acid; all studies reported that no cases of spontaneous osteonecrosis were observed during the course of the RCT. One reported that cases of osteonecrosis in both the zoledronic acid and placebo groups following dental surgery (one case in each group) resolved with antibiotic therapy.[7]

Carmona et.al. reported that less than 25% of ONJ cases occur spontaneously, with factors associated with its occurrence being mainly dental procedures and to a lesser extent defective dentures, trauma, bone exostosis and drug therapy (corticosteroids).[6]

Local Guidelines

South African Guidelines

The National Osteoporosis Foundation of South Africa (NOFSA) Guidelines indicate bisphosphonates (no formulation recommended) as first-line treatment for osteoporosis in postmenopausal women, men and in certain secondary osteoporosis like glucocorticoid-induced osteoporosis GIOP (GRADE1/ØØØØ – high quality recommendation). This

guideline also indicates that there is no apparent clear difference in the antifracture efficacy of the bisphosphonates registered in this country, alendronate, ibandronate, risedronate or zoledronate, and no particular bisphosphonate is, therefore, recommended.[1]

African Guidelines

The African Society of Bone Health and Metabolic Bone Disease indicates that where oral bisphosphonates are not tolerated or contraindicated, intravenous bisphosphonates (or denosumab) are the most appropriate alternatives. (Grade 2a)[9]

Cost comparison

Doses:

- Zoledronate 4mg/5mg IVI annually
- Ibandronate 3 mg IVI 3 monthly
- Risedronic acid 35 mg PO weekly

Product	Regimen	Available product	Cost per product	Cost per dose	Cost per month	Cost per dose 3 months regimen	Annual cost
Zoledronate	4mg IVI annually for 3 years	Zoledronic acid 4mg/5ml injection	R124.66*	R124.66		-	**R124.66**
Ibandronate	3mg IVI every 3 months	Ibandronic acid; 6mg; injection; 6 ml	R113.85*	R113.85 (half discarded)		R113.85	**R455.40**
Risedronic acid	35mg PO weekly	Risedronic Acid; 35mg; Tablet; 4 Tablets	R8.51**	R2.13	R8.51		**R102.12**

**New contract price taking effect 1 July 2024*
***MHPL February2024*

The management of osteoporosis with oral bisphosphonates is more affordable as compared to IV bisphosphonates. Zoledronate is currently the most affordable IV bisphosphonates, with an annual cost difference of approximately R20 per patient.

QUALITY

Overall quality of the evidence for efficacy was assessed as low. Evidence comprised only one post-hoc analysis of an RCT which was assessed to be of an 'unclear' risk of bias. Sub-group analyses were based on per protocol population from the Nakamuru et.al.[8] and furthermore it was unclear if a double dummy was utilised as there were different formulations assessed. However, all other domains were considered to be low risk of bias. Sub-group populations did meet the population of interest for the PICO specifically (T-score ≤-2.5) and as there was only one study heterogeneity was not a concern. For the safety, quality of evidence was considered very low based on a systematic literature review reporting on evidence from SRs, MAs and RCTs (AMSTAR 2 assessment: Critically low quality, as no meta-analysis done, rather reporting on others).

SUMMARY

Oral and IV bisphosphonates for secondary prevention; have been shown to be non-inferior to each other in terms of fracture prevention. Additionally there is no data to suggest that one IV alternative is superior to another. There may be a higher chance of ONJ with use of IV bisphosphonates as compared to oral, however this occurrence appears to be low. The benefits of using bisphosphonates outweigh the risk of adverse effects such as the rare complication of osteonecrosis of the jaw.

Oral bisphosphonates are more affordable, however the use of annual IV zoledronate is currently only slightly more costly than the oral alternatives.

RECOMMENDATIONS

It is recommended that IV bisphosphonates be considered for the secondary prevention of osteoporosis-associated fractures in patients who are unable to tolerate oral bisphosphonates, or where oral bisphosphonates are contraindicated. Currently the most affordable IV bisphosphonate option is zoledronate, largely due to its annual dosing, as compared to ibandronate that requires 3 monthly dosing.

Appendix 1: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ]	Only one post-hoc analysis of an RCT included, assessed as unclear risk of bias. Sub-group populations however did meet the population of interest specifically.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	Data shows non-inferiority between oral and IV bisphosphonates for fracture reduction. The vertebral fracture incidence was consistently lower, but not significantly so, with monthly IV ibandronate 1mg than with the other treatments, regardless of the baseline FN BMD T score. Incidence of non-vertebral fractures in the sub-groups of patients with FN BMD T Score < -2.5 and <-3 after 36 months was reported to be not significantly different [(HR IV ibandronate vs oral risedronate 0.87 (CI 0.39 – 1.94) and 0.74 (CI 0.27 -2.03) respectively].
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	One systematic literature review of SRs, MAs and RCTs
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	*Inconsistent reports of IV bisphosphonates causing more ONJ as compared to oral.*
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	*The use of IV bisphosphonates, particularly zoledronate which is dosed annually have the propensity to increase patient adherence and be more feasible to the patient and the health care facility.*

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: Uncertain:	**See costing section – minimal cost implications per patients.**
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: X Major: Uncertain: **Is the option acceptable to key stakeholders?** Yes: X No: Uncertain:	
EQUITY	**Would there be an impact on health inequity?** Yes: No: X Uncertain:	All products available on tender

Appendix 2: Search Strategy

Search	Query	Search Details	Results
#1	Intravenous AND oral AND osteoporosis AND bisphosphonates AND systematic reviews/meta-analyses	(("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("bisphosphonated"[All Fields] OR "bisphosphonic"[All Fields] OR "diphosphonates"[MeSH Terms] OR "diphosphonates"[All Fields] OR "bisphosphonate"[All Fields] OR "bisphosphonates"[All Fields]) AND ("osteoporosis"[MeSH Terms] OR "osteoporosis"[All Fields] OR "osteoporoses"[All Fields] OR "osteoporosis, postmenopausal"[MeSH Terms])) AND (meta-analysis[Filter] OR systematicreview[Filter])	37
#2	Intravenous AND oral AND osteoporosis AND bisphosphonates AND randomised controlled trial	(("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("bisphosphonated"[All Fields] OR "bisphosphonic"[All Fields] OR "diphosphonates"[MeSH Terms] OR "diphosphonates"[All Fields] OR "bisphosphonate"[All Fields] OR "bisphosphonates"[All Fields]) AND ("osteoporosis"[MeSH Terms] OR "osteoporosis"[All Fields] OR "osteoporoses"[All Fields] OR "osteoporosis, postmenopausal"[MeSH Terms])) AND (randomizedcontrolledtrial[Filter])	57

Appendix 3: Excluded studies

	Systematic reviews and meta-analyses	Reason for exclusion
1	The effectiveness of ibandronate in reducing the risk of nonvertebral fractures in women with osteoporosis: systematic review and meta-analysis of observational studies. Alves C, Mendes D, Penedones A, Oliveira T, Donato A, Batel-Marques F.Int J Clin Pharm. 2023 Dec 19. doi: 10.1007/s11096-023-01666-x.	**Does not meet PICO**
2	Cerebral palsy and bisphosphonates - and what can be learned from other types of secondary osteoporosis in children: A scoping review. Granild-Jensen JB, Pedersen LK, Langdahl B, Starup-Linde J, Rackauskaite G, Farholt S, Søndergaard C, Vestergaard ET, Møller-Madsen B.Acta Paediatr. 2023 Apr;112(4):617-629. doi: 10.1111/apa.16671. Epub 2023 Feb 1.PMID: 36644940 Review.	**Does not meet PICO**
3	Bisphosphonates for osteoporosis in people with cystic fibrosis. Jeffery TC, Chang AB, Conwell LS.Cochrane Database Syst Rev. 2023 Jan 10;1(1):CD002010. doi: 10.1002/14651858.CD002010.pub5.PMID: 36625789 Free PMC article. Review.	**Does not meet PICO**
4	Frequency of osteonecrosis in bisphosphonate users submitted to dental procedures: A systematic review. Martins LHI, Ferreira DC, Silva MT, Motta RHL, Franquez RT, Bergamaschi CC.Oral Dis. 2023 Jan;29(1):75-99. doi: 10.1111/odi.14003. Epub 2021 Sep 22.PMID: 34402147 Review.	**Does not meet PICO**
5	Reduced All-Cause Mortality With Bisphosphonates Among Post-Fracture Osteoporosis Patients: A Nationwide Study and Systematic Review. Hsu YH, Li CC, Liang FW, Peng ZY, Chang YF, Hsu JC, Ou HT, Wu CH.Clin Pharmacol Ther. 2022 Sep;112(3):711-719. doi: 10.1002/cpt.2645. Epub 2022 Jun 4.PMID: 35561128	**Does not meet PICO**
6	Interventions for managing medication-related osteonecrosis of the jaw. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O, Peter JU.Cochrane Database Syst Rev. 2022 Jul 12;7(7):CD012432. doi: 10.1002/14651858.CD012432.pub3.PMID: 35866376 Free PMC article. Review.	**Does not meet PICO**
7	Genome-wide Association Study Identified Chromosome 8 Locus Associated with Medication-Related Osteonecrosis of the Jaw. Yang G, Singh S, McDonough CW, Lamba JK, Hamadeh I, Holliday LS, Wang D, Katz J, Lakatos PA, Balla B, Kosa JP, Pelliccioni GA, Price DK, Van Driest SL, Figg WD, Langaee T, Moreb JS, Gong Y.Clin Pharmacol Ther. 2021 Dec;110(6):1558-1569. doi: 10.1002/cpt.2397. Epub 2021 Aug 31.PMID: 34390503 Free PMC article.	**Does not meet PICO**
8	Dental Implant Placement in Patients With a History of Medications Related to Osteonecrosis of the Jaws: A Systematic Review. Sher J, Kirkham-Ali K, Luo JD, Miller C, Sharma D.J Oral Implantol. 2021 Jun 1;47(3):249-268. doi: 10.1563/aaid-joi-D-19-00351.PMID: 32699903	**Does not meet PICO**
9	Bisphosphonate-associated osteonecrosis of the jaw. Ferreira Jr LH Jr, Mendonça Jr KD Jr, Chaves de Souza J, Soares Dos Reis DC, do Carmo Faleiros Veloso Guedes C, de Souza Castro Filice L, Bruzadelli Macedo S, Soares Rocha F.Minerva Dent Oral Sci. 2021 Feb;70(1):49-57. doi: 10.23736/S2724-6329.20.04306-X. Epub 2020 Sep 22.PMID: 32960522	**Does not meet PICO – look at treatment**
10	Efficacy and Safety of First- and Second-Line Drugs to Prevent Glucocorticoid-Induced Fractures.	**Does not meet PICO**

	Ding L, Hu J, Wang D, Liu Q, Mo Y, Tan X, Wen F.J Clin Endocrinol Metab. 2020 Jan 1;105(1):dgz023. doi: 10.1210/clinem/dgz023.PMID: 31513250	
11	Interventions for managing medication-related osteonecrosis of the jaw. Beth-Tasdogan NH, Mayer B, Hussein H, Zolk O.Cochrane Database Syst Rev. 2017 Oct 6;10(10):CD012432. doi: 10.1002/14651858.CD012432.pub2.PMID: 28983908 Free PMC article. Updated. Review.	**Does not meet PICO**
12	Surgical treatment vs. conservative treatment in intravenous bisphosphonate-related osteonecrosis of the jaws. Systematic review. Comas-Calonge A, Figueiredo R, Gay-Escoda C.J Clin Exp Dent. 2017 Feb 1;9(2):e302-e307. doi: 10.4317/jced.53504. eCollection 2017 Feb.PMID: 28210453 Free PMC article. Review.	**Does not meet PICO**
13	Interventions to prevent and treat corticosteroid-induced osteoporosis and prevent osteoporotic fractures in Duchenne muscular dystrophy. Bell JM, Shields MD, Watters J, Hamilton A, Beringer T, Elliott M, Quinlivan R, Tirupathi S, Blackwood B.Cochrane Database Syst Rev. 2017 Jan 24;1(1):CD010899. doi: 10.1002/14651858.CD010899.pub2.PMID: 28117876 Free PMC article. Review.	**Does not meet PICO**
14	Adjuvant bisphosphonates in early breast cancer: consensus guidance for clinical practice from a European Panel. Hadji P, Coleman RE, Wilson C, Powles TJ, Clézardin P, Aapro M, Costa L, Body JJ, Markopoulos C, Santini D, Diel I, Di Leo A, Cameron D, Dodwell D, Smith I, Gnant M, Gray R, Harbeck N, Thurlimann B, Untch M, Cortes J, Martin M, Albert US, Conte PF, Ejlertsen B, Bergh J, Kaufmann M, Holen I.Ann Oncol. 2016 Mar;27(3):379-90. doi: 10.1093/annonc/mdv617. Epub 2015 Dec 17.PMID: 26681681 Free article. Review.	**Does not meet PICO**
15	Dose-Effectiveness Relationships Determining the Efficacy of Ibandronate for Management of Osteoporosis: A Meta-Analysis. Hou Y, Gu K, Xu C, Ding H, Liu C, Tuoheti Y.Medicine (Baltimore). 2015 Jul;94(26):e1007. doi: 10.1097/MD.0000000000001007.PMID: 26131800 Free PMC article. Review.	**Does not meet PICO**
16	Treatment of glucocorticoid-induced low bone mineral density in children: a systematic review. Jayasena A, Atapattu N, Lekamwasam S.Int J Rheum Dis. 2015 Mar;18(3):287-93. doi: 10.1111/1756-185X.12560.PMID: 25923606 Review.	**Does not meet PICO**
17	Is there enough evidence to use bisphosphonates in HIV-infected patients? A systematic review and meta-analysis. Pinzone MR, Moreno S, Cacopardo B, Nunnari G.AIDS Rev. 2014 Oct-Dec;16(4):213-22.PMID: 25300622 Review.	**Does not meet PICO**
18	Risk of atrial fibrillation with use of oral and intravenous bisphosphonates. Sharma A, Einstein AJ, Vallakati A, Arbab-Zadeh A, Walker MD, Mukherjee D, Homel P, Borer JS, Lichstein E.Am J Cardiol. 2014 Jun 1;113(11):1815-21. doi: 10.1016/j.amjcard.2014.03.008. Epub 2014 Mar 15.PMID: 24837258 Review.	**Does not meet PICO**
19	Bisphosphonates for osteoporosis in people with cystic fibrosis. Conwell LS, Chang AB.Cochrane Database Syst Rev. 2014 Mar 14;2014(3):CD002010. doi: 10.1002/14651858.CD002010.pub4.PMID: 24627308 Free PMC article. Updated. Review.	**Does not meet PICO**
20	Risk of osteonecrosis in patients taking bisphosphonates for prevention of osteoporosis: a systematic review and meta-analysis. Lee SH, Chang SS, Lee M, Chan RC, Lee CC.Osteoporos Int. 2014 Mar;25(3):1131-9. doi: 10.1007/s00198-013-2575-3. Epub 2013 Dec 17.PMID: 24343364 Review.	**Does not meet PICO**
21	Long-term fracture rates seen with continued ibandronate treatment: pooled analysis of DIVA and MOBILE long-term extension studies. Miller PD, Recker RR, Harris S, Silverman S, Felsenberg D, Reginster J, Day BM, Barr C, Masanauskaite D.Osteoporos Int. 2014 Jan;25(1):349-57. doi: 10.1007/s00198-013-2518-z. Epub 2013 Oct 18.PMID: 24136103	**Does not meet PICO**
22	Effectiveness of bisphosphonate analogues and functional electrical stimulation on attenuating post-injury osteoporosis in spinal cord injury patients- a systematic review and meta-analysis. Chang KV, Hung CY, Chen WS, Lai MS, Chien KL, Han DS.PLoS One. 2013 Nov 22;8(11):e81124. doi: 10.1371/journal.pone.0081124. eCollection 2013.PMID: 24278386 Free PMC article. Review.	**Does not meet PICO**
23	Systematic literature review of bisphosphonates and osteonecrosis of the jaw in patients with osteoporosis. Chamizo Carmona E, Gallego Flores A, Loza Santamaría E, Herrero Olea A, Rosario Lozano MP.Reumatol Clin. 2013 May-Jun;9(3):172-7. doi: 10.1016/j.reuma.2012.05.005. Epub 2012 Jul 10.PMID: 22784630 Free article. Review. English, Spanish.	**Duplicate and included**
24	Bisphosphonates for osteoporosis in nonmetastatic prostate cancer patients receiving androgen-deprivation therapy: a systematic review and meta-analysis. Ding H, Yang L, Du W, Teng Y, Fu SJ, Tao Y, Lu JZ, Wang ZP.Asian Pac J Cancer Prev. 2013;14(5):3337-43. doi: 10.7314/apjcp.2013.14.5.3337.PMID: 23803126 Free article. Review.	**Does not meet PICO**
25	Bisphosphonates for osteoporosis in people with cystic fibrosis. Conwell LS, Chang AB.Cochrane Database Syst Rev. 2012 Apr 18;(4):CD002010. doi: 10.1002/14651858.CD002010.pub3.PMID: 22513903 Updated. Review.	**Does not meet PICO**
26	Evidence of sustained vertebral and nonvertebral antifracture efficacy with ibandronate therapy: a systematic review. Adami S, Idolazzi L, Rossini M.Ther Adv Musculoskelet Dis. 2011 Apr;3(2):67-79. doi: 10.1177/1759720X10395651.PMID: 22870467 Free PMC article.	**Does not meet PICO**
27	Impact of cystic fibrosis on bone health. Haworth CS.Curr Opin Pulm Med. 2010 Nov;16(6):616-22. doi: 10.1097/MCP.0b013e32833e2e94.PMID: 20739891 Review.	**Does not meet PICO**
28	Ibandronate does not increase risk of atrial fibrillation in analysis of pivotal clinical trials. Lewiecki EM, Cooper C, Thompson E, Hartl F, Mehta D, Papapoulos SE.Int J Clin Pract. 2010 May;64(6):821-6. doi: 10.1111/j.1742-1241.2010.02335.x. Epub 2010 Mar 11.PMID: 20337751 Review.	**Does not meet PICO**

29	Bisphosphonates for osteoporosis in people with cystic fibrosis. Conwell LS, Chang AB.Cochrane Database Syst Rev. 2009 Oct 7;(4):CD002010. doi: 10.1002/14651858.CD002010.pub2.PMID: 19821288 Updated. Review.	**Does not meet PICO**
30	What impact do systemically administrated bisphosphonates have on oral implant therapy? A systematic review. Madrid C, Sanz M.Clin Oral Implants Res. 2009 Sep;20 Suppl 4:87-95. doi: 10.1111/j.1600-0501.2009.01772.x.PMID: 19663954 Review.	**Does not meet PICO**
31	Bisphosphonate associated osteonecrosis of the jaw. Khan AA, Sándor GK, Dore E, Morrison AD, Alsahli M, Amin F, Peters E, Hanley DA, Chaudry SR, Lentle B, Dempster DW, Glorieux FH, Neville AJ, Talwar RM, Clokie CM, Mardini MA, Paul T, Khosla S, Josse RG, Sutherland S, Lam DK, Carmichael RP, Blanas N, Kendler D, Petak S, Ste-Marie LG, Brown J, Evans AW, Rios L, Compston JE; Canadian Taskforce on Osteonecrosis of the Jaw.	**Does not meet PICO**
32	Factors associated with osteonecrosis of the jaw among bisphosphonate users. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS.Am J Med. 2008 Jun;121(6):475-483.e3. doi: 10.1016/j.amjmed.2008.01.047.PMID: 18501224 Free PMC article. Review.	**Does not meet PICO**
33	Ibandronate and the risk of non-vertebral and clinical fractures in women with postmenopausal osteoporosis: results of a meta-analysis of phase III studies. Harris ST, Blumentals WA, Miller PD.Curr Med Res Opin. 2008 Jan;24(1):237-45. doi: 10.1185/030079908x253717.PMID: 18047776	**Does not meet PICO**
34	Bisphosphonate therapy for children and adolescents with secondary osteoporosis. Ward L, Tricco AC, Phuong P, Cranney A, Barrowman N, Gaboury I, Rauch F, Tugwell P, Moher D.Cochrane Database Syst Rev. 2007 Oct 17;2007(4):CD005324. doi: 10.1002/14651858.CD005324.pub2.PMID: 17943849 Free PMC article. Review.	**Does not meet PICO**
35	A semimechanistic and mechanistic population PK-PD model for biomarker response to ibandronate, a new bisphosphonate for the treatment of osteoporosis. Pillai G, Gieschke R, Goggin T, Jacqmin P, Schimmer RC, Steimer JL.Br J Clin Pharmacol. 2004 Dec;58(6):618-31. doi: 10.1111/j.1365-2125.2004.02224.x.PMID: 15563360	**Does not meet PICO**
36	Bisphosphonates for osteoporosis in people with cystic fibrosis. Brenckmann C, Papaioannou A.Cochrane Database Syst Rev. 2001;(4):CD002010. doi: 10.1002/14651858.CD002010.PMID: 11687132 Updated. Review.	**Does not meet PICO**

	Randomised controlled trials	**Reason for exclusion**
1	Cost Analysis of a Fracture Liaison Service: A Randomized Controlled Trial for the Secondary Prevention After Fragility Fractures of the Hip. Zinger G, Davidson A, Sylvetsky N, Levy Y, Peyser A.Endocr Pract. 2023 Oct;29(10):794-802. doi: 10.1016/j.eprac.2023.07.030. Epub 2023 Aug 2.PMID: 37541586 Clinical Trial.	**Does not meet PICO**
2	Effect of a Three-Day Course of Dexamethasone on Acute Phase Response Following Treatment With Zoledronate: A Randomized Controlled Trial. Murdoch R, Mellar A, Horne AM, Billington E, Chan PL, Gamble GD, Reid IR.J Bone Miner Res. 2023 May;38(5):631-638. doi: 10.1002/jbmr.4802. Epub 2023 Apr 9.PMID: 36970850 Clinical Trial.	**Does not meet PICO**
3	Efficacy and safety of denosumab vs. **bisphosphonates** in postmenopausal women previously treated with **oral bisphosphonates**. Miller PD, Pannacciulli N, Malouf-Sierra J, Singer A, Czerwiński E, Bone HG, Wang C, Huang S, Chines A, Lems W, Brown JP.Osteoporos Int. 2020 Jan;31(1):181-191. doi: 10.1007/s00198-019-05233-x. Epub 2019 Nov 28.PMID: 31776637 Clinical Trial.	**Does not meet PICO**
4	Comparison of BMD Changes and Bone Formation Marker Levels 3 Years After **Bisphosphonate** Discontinuation: FLEX and HORIZON-PFT Extension I Trials. Kim TY, Bauer DC, McNabb BL, Schafer AL, Cosman F, Black DM, Eastell R.J Bone Miner Res. 2019 May;34(5):810-816. doi: 10.1002/jbmr.3654. Epub 2019 Jan 15.PMID: 30536713 **Free PMC article.** Clinical Trial.	**Does not meet PICO**
5	Comparative adherence to weekly **oral** and quarterly **intravenous bisphosphonates** among patients with limited heath literacy who sustained distal radius fractures. Roh YH, Noh JH, Gong HS, Baek GH.J Bone Miner Metab. 2018 Sep;36(5):589-595. doi: 10.1007/s00774-017-0867-y. Epub 2017 Oct 5.PMID: 28983705 Clinical Trial.	**Does not meet PICO – wrong outcome**
6	Monthly **oral** ibandronate 100 mg is as effective as monthly **intravenous** ibandronate 1 mg in patients with various pathologies in the MOVEST study. Hagino H, Ito M, Hashimoto J, Yamamoto M, Endo K, Katsumata K, Asao Y, Matsumoto R, Nakano T, Mizunuma H, Nakamura T.J Bone Miner Metab. 2018 May;36(3):336-343. doi: 10.1007/s00774-017-0839-2. Epub 2017 Apr 7.PMID: 28389932 Clinical Trial.	**Does not meet PICO – wrong outcome**
7	Effect of single-dose dexamethasone on acute phase response following zoledronic acid: a randomized controlled trial. Billington EO, Horne A, Gamble GD, Maslowski K, House M, Reid IR.Osteoporos Int. 2017 Jun;28(6):1867-1874. doi: 10.1007/s00198-017-3960-0. Epub 2017 Feb 23.PMID: 28233020 Clinical Trial.	**Does not meet PICO**
8	Efficacy and safety of once-yearly zoledronic acid in Japanese patients with primary **osteoporosis**: two-year results from a randomized placebo-controlled double-blind study (Zoledronate treatment in Efficacy to **osteoporosis**; ZONE study). Nakamura T, Fukunaga M, Nakano T, Kishimoto H, Ito M, Hagino H, Sone T, Taguchi A, Tanaka S, Ohashi M, Ota Y, Shiraki M.Osteoporos Int. 2017 Jan;28(1):389-398. doi: 10.1007/s00198-016-3736-y. Epub 2016 Sep 8.PMID: 27631091 **Free PMC article.** Clinical Trial.	**Does not meet PICO**

9	Higher response with bone mineral density increase with monthly injectable ibandronate 1 mg compared with **oral** risedronate in the MOVER study. Nakano T, Yamamoto M, Hashimoto J, Tobinai M, Yoshida S, Nakamura T.J Bone Miner Metab. 2016 Nov;34(6):678-684. doi: 10.1007/s00774-015-0717-8. Epub 2015 Oct 13.PMID: 26462480 Clinical Trial.	**Does not meet PICO – wrong outcome**
10	The optimal **oral** dose selection of ibandronate in Japanese patients with **osteoporosis** based on pharmacokinetic and pharmacodynamic properties. Nakai K, Tobinai M, Hashimoto J, Iida S, Kawanishi T.Eur J Drug Metab Pharmacokinet. 2016 Apr;41(2):139-47. doi: 10.1007/s13318-014-0242-5. Epub 2014 Dec 5.PMID: 25476995 **Free PMC article.** Clinical Trial.	**Does not meet PICO**
11	Clinical efficacy and safety of monthly **oral** ibandronate 100 mg versus monthly **intravenous** ibandronate 1 mg in Japanese patients with primary **osteoporosis**. Nakamura T, Ito M, Hashimoto J, Shinomiya K, Asao Y, Katsumata K, Hagino H, Inoue T, Nakano T, Mizunuma H; MOVEST Study Group.Osteoporos Int. 2015 Nov;26(11):2685-93. doi: 10.1007/s00198-015-3175-1. Epub 2015 May 23.PMID: 26001561 **Free PMC article.** Clinical Trial.	**Does not meet PICO**
12	Cost-minimization study comparing annual infusion of zoledronic acid or weekly **oral** alendronate in women with low bone mineral density. Chávez-Valencia V, Arce-Salinas CA, Espinosa-Ortega F.J Clin Densitom. 2014 Oct-Dec;17(4):484-9. doi: 10.1016/j.jocd.2013.12.001. Epub 2014 Mar 5.PMID: 24613450 Clinical Trial.	**Does not meet PICO – wrong outcome**
13	Clinical efficacy on fracture risk and safety of 0.5 mg or 1 mg/month **intravenous** ibandronate versus 2.5 mg/day **oral** risedronate in patients with primary **osteoporosis**. Nakamura T, Nakano T, Ito M, Hagino H, Hashimoto J, Tobinai M, Mizunuma H; MOVER Study Group.Calcif Tissue Int. 2013 Aug;93(2):137-46. doi: 10.1007/s00223-013-9734-6. Epub 2013 May 5.PMID: 23644930 **Free PMC article.** Clinical Trial.	**Does not meet PICO**
14	Intramuscular neridronate in patients with rheumatoid arthritis using corticosteroids: evaluation of treatment adherence in a randomized, open-label comparison with other **bisphosphonates**. Muratore M, Quarta E, Quarta L.Acta Biomed. 2013 Jun 1;84(1):23-9.PMID: 24189759 Clinical Trial.	**Does not meet PICO**
15	Effect on bone turnover markers of once-yearly **intravenous** infusion of zoledronic acid versus daily **oral** risedronate in patients treated with glucocorticoids. Devogelaer JP, Sambrook P, Reid DM, Goemaere S, Ish-Shalom S, Collette J, Su G, Bucci-Rechtweg C, Papanastasiou P, Reginster JY.Rheumatology (Oxford). 2013 Jun;52(6):1058-69. doi: 10.1093/rheumatology/kes410. Epub 2013 Jan 30.PMID: 23365149 Clinical Trial.	**Does not meet PICO**
16	Efficacy of a combined alendronate and calcitriol agent (Maxmarvil®) in Korean postmenopausal women with early breast cancer receiving aromatase inhibitor: a double-blind, randomized, placebo-controlled study. Rhee Y, Song K, Park S, Park HS, Lim SK, Park BW.Endocr J. 2013;60(2):167-72. doi: 10.1507/endocrj.ej12-0283. Epub 2012 Oct 13.PMID: 23064476 **Free article.** Clinical Trial.	**Does not meet PICO**
17	A 1-year randomized, double-blind, placebo-controlled study of **intravenous** ibandronate on bone loss following renal transplantation. Smerud KT, Dolgos S, Olsen IC, Åsberg A, Sagedal S, Reisæter AV, Midtvedt K, Pfeffer P, Ueland T, Godang K, Bollerslev J, Hartmann A.Am J Transplant. 2012 Dec;12(12):3316-25. doi: 10.1111/j.1600-6143.2012.04233.x. Epub 2012 Sep 4.PMID: 22946930 **Free article.** Clinical Trial.	**Does not meet PICO**
18	A multicenter randomized double-masked comparative study of different preparations of alendronate in **osteoporosis** - monthly (four weeks) **intravenous** versus once weekly **oral** administrations. Shiraki M, Nakamura T, Fukunaga M, Sone T, Usami A, Inoue T.Curr Med Res Opin. 2012 Aug;28(8):1357-67. doi: 10.1185/03007995.2012.709838. Epub 2012 Jul 20.PMID: 22769235 Clinical Trial.	**Does not meet PICO**
19	Quality of life and health status with zoledronic acid and generic alendronate--a secondary analysis of the Rapid Onset and Sustained Efficacy (ROSE) study in postmenopausal women with low bone mass. Hadji P, Ziller V, Gamerdinger D, Spieler W, Articus K, Baier M, Moericke R, Kann PH.Osteoporos Int. 2012 Jul;23(7):2043-51. doi: 10.1007/s00198-011-1834-4. Epub 2011 Nov 16.PMID: 22086310 Clinical Trial.	**Does not meet PICO**
20	Long-term administration of quarterly IV ibandronate is effective and well tolerated in postmenopausal **osteoporosis**: 5-year data from the DIVA study long-term extension. Bianchi G, Czerwinski E, Kenwright A, Burdeska A, Recker RR, Felsenberg D.Osteoporos Int. 2012 Jun;23(6):1769-78. doi: 10.1007/s00198-011-1793-9.PMID: 21975558 Clinical Trial.	**Does not meet PICO**
21	Post hoc analysis of a single IV infusion of zoledronic acid versus daily **oral** risedronate on lumbar spine bone mineral density in different subgroups with glucocorticoid-induced **osteoporosis**. Roux C, Reid DM, Devogelaer JP, Saag K, Lau CS, Reginster JY, Papanastasiou P, Bucci-Rechtweg C, Su G, Sambrook PN.Osteoporos Int. 2012 Mar;23(3):1083-90. doi: 10.1007/s00198-011-1800-1.PMID: 21975559 Clinical Trial.	**Does not meet PICO – wrong design**
22	Rapid Onset and Sustained Efficacy (ROSE) study: results of a randomised, multicentre trial comparing the effect of zoledronic acid or alendronate on bone metabolism in postmenopausal women with low bone mass. Hadji P, Gamerdinger D, Spieler W, Kann PH, Loeffler H, Articus K, Möricke R, Ziller V.Osteoporos Int. 2012 Feb;23(2):625-33. doi: 10.1007/s00198-011-1583-4. Epub 2011 Mar 26.PMID: 21442459 Clinical Trial.	**Does not meet PICO**
23	Treatment with acetaminophen/paracetamol or ibuprofen alleviates post-dose symptoms related to **intravenous** infusion with zoledronic acid 5 mg. Wark JD, Bensen W, Recknor C, Ryabitseva O, Chiodo J 3rd, Mesenbrink P, de Villiers TJ.Osteoporos Int. 2012 Feb;23(2):503-12. doi: 10.1007/s00198-011-1563-8. Epub 2011 Feb 19.PMID: 21331467 Clinical Trial.	**Does not meet PICO**
24	Effects of **intravenous** ibandronate injection on renal function in women with postmenopausal **osteoporosis** at high risk for renal disease--the DIVINE study. Miller PD, Ragi-Eis S, Mautalen C, Ramirez F, Jonkanski I.Bone. 2011 Dec;49(6):1317-22. doi: 10.1016/j.bone.2011.09.035. Epub 2011 Sep 16.PMID: 21945737 Clinical Trial.	**Does not meet PICO**
25	Comparison of alendronate and pamidronate on bone loss in kidney transplant patients for the first 6 months of transplantation.	**Does not meet PICO**

	Omidvar B, Ghorbani A, Shahbazian H, Beladi Mousavi SS, Shariat Nabavi SJ, Alasti M.Iran J Kidney Dis. 2011 Nov;5(6):420-4.PMID: 22057076 **Free article.** Clinical Trial.	
26	**Bisphosphonate**-related osteonecrosis: laser-assisted surgical treatment or conventional surgery? Atalay B, Yalcin S, Emes Y, Aktas I, Aybar B, Issever H, Mandel NM, Cetin O, Oncu B.Lasers Med Sci. 2011 Nov;26(6):815-23. doi: 10.1007/s10103-011-0974-2. Epub 2011 Aug 2.PMID: 21809068 Clinical Trial.	**Does not meet PICO**
27	Effect of zoledronic acid compared with raloxifene on bone turnover markers in postmenopausal women with low bone density. Bachmann G, Kriegman A, Gonçalves J, Kianifard F, Warren M, Simon JA.Menopause. 2011 Aug;18(8):851-6. doi: 10.1097/gme.0b013e31820b80f1.PMID: 21796066 Clinical Trial.	**Does not meet PICO**
28	Increases in hip and spine bone mineral density are predictive for vertebral antifracture efficacy with ibandronate. Miller PD, Delmas PD, Huss H, Patel KM, Schimmer RC, Adami S, Recker RR.Calcif Tissue Int. 2010 Oct;87(4):305-13. doi: 10.1007/s00223-010-9403-y. Epub 2010 Aug 25.PMID: 20737140 Clinical Trial.	**Does not meet PICO**
29	Characterization of and risk factors for the acute-phase response after zoledronic acid. Reid IR, Gamble GD, Mesenbrink P, Lakatos P, Black DM.J Clin Endocrinol Metab. 2010 Sep;95(9):4380-7. doi: 10.1210/jc.2010-0597. Epub 2010 Jun 16.PMID: 20554708 Clinical Trial.	**Does not meet PICO**
30	Infusion of ibandronate once every 3 months effectively decreases bone resorption markers and increases bone mineral density in Chinese postmenopausal osteoporotic women: a 1-year study. Li M, Xing XP, Zhang ZL, Liu JL, Zhang ZL, Liu DG, Xia WB, Meng XW.J Bone Miner Metab. 2010 May;28(3):299-305. doi: 10.1007/s00774-009-0126-y. Epub 2009 Oct 24.PMID: 19855926 Clinical Trial.	**Does not meet PICO**
31	Effects of intermittent **intravenous** ibandronate injections on bone quality and micro-architecture in women with postmenopausal **osteoporosis**: the DIVA study. Recker RR, Ste-Marie LG, Langdahl B, Czerwinski E, Bonvoisin B, Masanauskaite D, Rowell L, Felsenberg D.Bone. 2010 Mar;46(3):660-5. doi: 10.1016/j.bone.2009.11.004. Epub 2009 Nov 10.PMID: 19909829 Clinical Trial.	**Does not meet PICO**
32	Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced **osteoporosis** (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. Reid DM, Devogelaer JP, Saag K, Roux C, Lau CS, Reginster JY, Papanastasiou P, Ferreira A, Hartl F, Fashola T, Mesenbrink P, Sambrook PN; HORIZON investigators.Lancet. 2009 Apr 11;373(9671):1253-63. doi: 10.1016/S0140-6736(09)60250-6.PMID: 19362675 Clinical Trial.	**Does not meet PICO**
33	Intramuscular neridronate in postmenopausal women with low bone mineral density. Adami S, Gatti D, Bertoldo F, Sartori L, Di Munno O, Filipponi P, Marcocci C, Frediani B, Palummeri E, Fiore CE, Costi D, Rossini M.Calcif Tissue Int. 2008 Nov;83(5):301-7. doi: 10.1007/s00223-008-9179-5. Epub 2008 Oct 23.PMID: 18946626 Clinical Trial.	**Does not meet PICO**
34	Efficacy and tolerability of **intravenous** ibandronate injections in postmenopausal **osteoporosis**: 2-year results from the DIVA study. Eisman JA, Civitelli R, Adami S, Czerwinski E, Recknor C, Prince R, Reginster JY, Zaidi M, Felsenberg D, Hughes C, Mairon N, Masanauskaite D, Reid DM, Delmas PD, Recker RR.J Rheumatol. 2008 Mar;35(3):488-97. Epub 2008 Feb 1.PMID: 18260172 Clinical Trial.	**Does not meet PICO**
35	Incidence of osteonecrosis of the jaw in women with postmenopausal **osteoporosis** in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. Grbic JT, Landesberg R, Lin SQ, Mesenbrink P, Reid IR, Leung PC, Casas N, Recknor CP, Hua Y, Delmas PD, Eriksen EF; Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial Research Group.J Am Dent Assoc. 2008 Jan;139(1):32-40. doi: 10.14219/jada.archive.2008.0017.PMID: 18167382 Clinical Trial.	**Does not meet PICO**
36	A double-blind placebo-controlled study of **intravenous** clodronate for prevention of steroid-induced bone loss in inflammatory bowel disease. Abitbol V, Briot K, Roux C, Roy C, Seksik P, Charachon A, Bouhnik Y, Coffin B, Allez M, Lamarque D, Chaussade S.Clin Gastroenterol Hepatol. 2007 Oct;5(10):1184-9. doi: 10.1016/j.cgh.2007.05.016. Epub 2007 Aug 1.PMID: 17683996 Clinical Trial.	**Does not meet PICO**
37	**Intravenous** zoledronic acid 5 mg in the treatment of postmenopausal women with low bone density previously treated with alendronate. McClung M, Recker R, Miller P, Fiske D, Minkoff J, Kriegman A, Zhou W, Adera M, Davis J.Bone. 2007 Jul;41(1):122-8. doi: 10.1016/j.bone.2007.03.011. Epub 2007 Mar 24.PMID: 17468062 Clinical Trial.	**Does not meet PICO -wrong outcome**
38	[Fracture prevention in postmenopausal women with **osteoporosis** by an annual infusion of zoledronic acid]. Geusens PP, Lems WF.Ned Tijdschr Geneeskd. 2007 Jun 30;151(26):1445-8.PMID: 17633971 Clinical Trial. Dutch.	**Does not meet PICO**
39	A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly **oral** alendronate in postmenopausal women with low bone mineral density. Saag K, Lindsay R, Kriegman A, Beamer E, Zhou W.Bone. 2007 May;40(5):1238-43. doi: 10.1016/j.bone.2007.01.016. Epub 2007 Feb 8.PMID: 17347063 Clinical Trial.	**Does not meet PICO -wrong outcome**
40	**Intravenous** ibandronate injections in postmenopausal women with **osteoporosis**: one-year results from the dosing **intravenous** administration study. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, Christiansen C, Civitelli R, Drezner MK, Recker RR, Bolognese M, Hughes C, Masanauskaite D, Ward P, Sambrook P, Reid DM.Arthritis Rheum. 2006 Jun;54(6):1838-46. doi: 10.1002/art.21918.PMID: 16729277 **Free article.** Clinical Trial.	**Does not meet PICO -wrong outcome**
41	Impact of alendronate on quality of life in children with osteogenesis imperfecta. Seikaly MG, Kopanati S, Salhab N, Waber P, Patterson D, Browne R, Herring JA.J Pediatr Orthop. 2005 Nov-Dec;25(6):786-91. doi: 10.1097/01.bpo.0000176162.78980.ed.PMID: 16294137 Clinical Trial.	**Does not meet PICO**
42	Effective doses of ibandronate do not influence the 3-year progression of aortic calcification in elderly osteoporotic women. Tankó LB, Qin G, Alexandersen P, Bagger YZ, Christiansen C.Osteoporos Int. 2005 Feb;16(2):184-90. doi: 10.1007/s00198-004-1662-x. Epub 2004 Jun 10.PMID: 15197541 Clinical Trial.	**Does not meet PICO**

43	Efficacy and safety of ibandronate given by **intravenous** injection once every 3 months. Adami S, Felsenberg D, Christiansen C, Robinson J, Lorenc RS, Mahoney P, Coutant K, Schimmer RC, Delmas PD.Bone. 2004 May;34(5):881-9. doi: 10.1016/j.bone.2004.01.007.PMID: 15121020 Clinical Trial.	**Does not meet PICO**
44	A randomized controlled trial of calcium with vitamin D, alone or in combination with **intravenous** pamidronate, for the treatment of low bone mineral density associated with Crohn's disease. Bartram SA, Peaston RT, Rawlings DJ, Francis RM, Thompson NP.Aliment Pharmacol Ther. 2003 Dec;18(11-12):1121-7. doi: 10.1111/j.1365-2036.2003.01794.x.PMID: 14653832 **Free article.** Clinical Trial.	**Does not meet PICO**
45	**Intravenous** ibandronate injections given every three months: a new treatment option to prevent bone loss in postmenopausal women. Stakkestad JA, Benevolenskaya LI, Stepan JJ, Skag A, Nordby A, Oefjord E, Burdeska A, Jonkanski I, Mahoney P; Ibandronate Intravenous Study Group.Ann Rheum Dis. 2003 Oct;62(10):969-75. doi: 10.1136/ard.62.10.969.PMID: 12972476 **Free PMC article.** Clinical Trial.	**Does not meet PICO**
46	**Intravenous** intermittent neridronate in the treatment of postmenopausal **osteoporosis**. Braga V, Gatti D, Colapietro F, Battaglia E, Righetti D, Prizzi R, Rossini M, Adami S.Bone. 2003 Sep;33(3):342-5. doi: 10.1016/s8756-3282(03)00084-x.PMID: 13678775 Clinical Trial.	**Does not meet PICO**
47	Response to alendronate in osteoporotic women previously treated with pamidronate. Peretz A, Siderova V, Body JJ, Dumon JC, Rozenberg S, Fellemans C, Fuss M, Bergmann P; Interdisciplinary Group for the Study of Bone Diseases and Calcium metabolism (GIPOB).Maturitas. 2003 Feb 25;44(2):111-5. doi: 10.1016/s0378-5122(02)00318-3.PMID: 12590006 Clinical Trial.	**Does not meet PICO**
48	**Intravenous** zoledronic acid in postmenopausal women with low bone mineral density. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, Widmer A, Devogelaer JP, Kaufman JM, Jaeger P, Body JJ, Brandi ML, Broell J, Di Micco R, Genazzani AR, Felsenberg D, Happ J, Hooper MJ, Ittner J, Leb G, Mallmin H, Murray T, Ortolani S, Rubinacci A, Saaf M, Samsioe G, Verbruggen L, Meunier PJ.N Engl J Med. 2002 Feb 28;346(9):653-61. doi: 10.1056/NEJMoa011807.PMID: 11870242 **Free article.** Clinical Trial.	**Does not meet PICO**
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50	Prevention of appendicular bone loss in Paget's disease following treatment with **intravenous** pamidronate disodium. Stewart GO, Gutteridge DH, Price RI, Ward L, Retallack RW, Prince RL, Stuckey BG, Kent GN, Bhagat CI, Dhaliwal SS.Bone. 1999 Feb;24(2):139-44. doi: 10.1016/s8756-3282(98)00163-x.PMID: 9951784 Clinical Trial.	**Does not meet PICO**
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