Bisphosphonate therapy: When *not* to monitor BMD. *J Fam Pract.* 2009;58:594-596.

Potential PURL Review Form: Randomized controlled trials

SECTION 1: IDENTIFYING INFORMATION

1. Citation	Bell KJ, Hayen A, Macaskill P, et al. Value of routine monitoring of bone mineral density after starting bisphosphonate treatment: secondary analysis of trial data. *BMJ*. 2009;338:b2266.
2. Hypertext link to PDF of full article	http://www.bmj.com/cgi/reprint/338/jun23_2/b2266
3. First date published study available to readers	July 23, 2009
4. PubMed ID	19549996
5. Nominated By	Sarah-Anne Schumann
6. Institutional Affiliation of Nominator	University of Chicago
7. Date Nominated	July 23, 2009
8. Identified Through	UpToDate
9. PURLS Editor Reviewing Nominated Potential PURL	Bernard Ewigman
10. Nomination Decision Date	July 24, 2009
11. Potential PURL Review Form (PPRF) Type	Randomized controlled trial (RCT)
12. Other comments, materials, or discussion	Secondary analysis; original Fracture Intervention Trial (FIT) study reviewed by U.S. as well: http://www.springerlink.com/content/h424864232000204/fulltext.pdf
13. Assigned Potential PURL Reviewer	Umang Sharma
14. Reviewer Affiliation	University of Chicago
15. Date Review Due	July 30, 2009
16. Abstract	**OBJECTIVE:** To assess the value of monitoring response to bisphosphonate treatment by means of measuring bone mineral density (BMD). **DESIGN:** Secondary analysis of trial data using mixed models. **DATA SOURCE:** The Fracture Intervention Trial, an RCT that compared the effects of alendronate and placebo in 6459 postmenopausal women with low BMD recruited between May 1992 and May 1993. Bone density measurements of hip and spine were obtained at baseline and at 1, 2, and 3 years after randomization. **MAIN OUTCOME MEASURES:** Between-person (treatment related) variation and within-person (measurement related) variation in hip and spine BMD. **RESULTS:** The mean effect of 3 years' treatment with alendronate was to increase hip BMD by 0.030 g/cm^2. There was some between-person variation in the effects of alendronate, but this was small in size compared with within-person variation. Alendronate treatment is estimated to result in increases in hip bone density ≥0.019 g/cm^2 in 97.5% of patients. **CONCLUSIONS:** Monitoring BMD in postmenopausal women in the first 3 years after starting treatment with a potent bisphosphonate is unnecessary and may

	be misleading. Routine monitoring should be avoided in this early period after bisphosphonate treatment is commenced.
17. Pending PURL Review Date	July 30, 2009

SECTION 2: CRITICAL APPRAISAL OF VALIDITY

1. Number of patients starting each arm of the study?	6459 total: 2027 with vertebral fracture (fx) detected at baseline by x-ray 4432 pwithout baseline fx ("clinical fx" group: followed for development of clinical fx) Within each group, patients were randomized to placebo or alendronate as below
2. Main characteristics of study patients (inclusions, exclusions, demographics, settings, etc.)?	Postmenopausal women with low BMD (<0.68 g/cm^2 at baseline, which is approximately 2 standard deviations below peak female BMD)
3. Intervention(s) being investigated?	Alendronate 5 mg/d for first 2 years, then increased to 10 mg/d when other data came out suggesting this dose had a greater effect. In both groups, participants thought to have insufficient calcium intake were advised to take calcium 500 mg/d and vitamin D 250 IU/d.
4. Comparison treatment(s), placebo, or nothing?	Identical placebo.
5. Length of follow up? Note specified end points e.g. death, cure, etc.	3 years; baseline and yearly bone density measurement.
6. What outcome measures are used? List all that assess effectiveness.	Between-person variation (treatment-related) compared with within-person variation (testing-related). Mean effect of placebo: BMD decrease 0.004 g/cm^2 per year (*P*<.001). Mean effect of alendronate for 1 year: BMD increase of 0.013 g/cm^2 (*P*<.001). Comparison of mean effect of time in alendronate group with placebo group: increase in BMD of 0.0085 g/cm^2 per year (*P*<.001). Between-person variation (treatment-related) was smaller than within-person variation, hence the authors concluded the treatment effect is relatively predictable and need not be monitored. After 3 years of treatment, hip BMD increased by 0.019 g/cm^2 in 98% of pts—a level of improvement that would encourage providers to recommend continuation. Standard deviation of between-person variation in treatment effect was 0.006 g/cm^2 for hip and 0.007 g/cm^2 for spine.
7. What is the effect of the intervention(s)? Include absolute risk, relative risk, NNT, CI, p-values, etc.	As above.
8. Study addresses an appropriate and clearly focused question - ***select one***	Adequately addressed
9. Random allocation to comparison groups	Adequately addressed Comments: discussed in the original FIT paper.

10. Concealed allocation to comparison groups	Adequately addressed Comments: see above
11. Subjects and investigators kept “blind” to comparison group allocation	Poorly addressed Comments: see above
12. Comparison groups are similar at the start of the trial	Adequately addressed Comments: see above
13. Were there any differences between the groups/arms of the study other than the intervention under investigation? If yes, please indicate whether the differences are a potential source of bias.	Adequately addressed Comments: see above.
14. Were all relevant outcomes measured in a standardized, valid, and reliable way?	Well covered
15. Are patient-oriented outcomes included? If yes, what are they?	No (only BMD).
16. What percent dropped out, and were lost to follow up? Could this bias the results? How?	Not discussed.
17. Was there an intention-to-treat analysis? If not, could this bias the results? How?	Yes
18. If a multi-site study, are results comparable for all sites?	N/A
19. Is the funding for the trial a potential source of bias? If yes, what measures were taken to insure scientific integrity?	No. Funded by Australian National Health and Medical Research Council. FIT trial sponsored by Merck. Neither had influence into any aspect of study.
20. To which patients might the findings apply? Include patients in the study and other patients to whom the findings may be generalized.	Postmenopausal women with osteoporosis receiving treatment with bisphosphonates.
21. In what care settings might the findings apply, or not apply?	Primary care

22. To which clinicians or policy makers might the findings be relevant?	Same

SECTION 3: REVIEW OF SECONDARY LITERATURE

1. DynaMed excerpts

2. DynaMed citation/access date	Alendronate. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: July 17, 2009. Accessed July 26, 2009.
3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)	Routine follow-up DEXA testing may not be needed until >3 years after treatment initiation.
4. UpToDate excerpts	
5. UpToDate citation/access date	Rosen HN, Marc K Drezner MK. Overview of the management of osteoporosis in postmenopausal women. In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. Last updated: May 27, 2009. Accessed July 26, 2009.
6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)	Follow-up DEXA should be performed in 1 year and less frequently thereafter if BMD stable or improved.
7. PEPID PCP excerpts	How should a DEXA scan be used to evaluate bisphosphonate therapy for osteoporosis? Evidence-Based Answer (Published January 2005) If bone density is evaluated after initiating bisphosphonate therapy, it should be tested no earlier than 2 years (strength of recommendation [SOR]: B, based on case series of dual energy x-ray absorptiometry [DEXA] scanning precision and bisphosphonate efficacy). • Currently no prospective, randomized trials investigate the impact of bone density follow-up testing on osteoporotic patients receiving bisphosphonate therapy. Evidence Summary 1. Testing the effectiveness of therapy for osteoporosis by measuring changes in BMD is difficult because changes are often small and occur slowly, and a decrease in BMD does not necessarily mean treatment failure. • Testing patients after starting bisphosphonate therapy has been part of many drug trials to assess the effectiveness of therapy. • Follow-up testing in clinical practice has not been the focus of a prospective trial and therefore remains controversial. 2. DEXA is considered the gold standard because it is the most extensively validated test for predicting fracture outcomes. • Understanding the rate of bone density response to therapy and the precision error of DEXA helps to determine monitoring intervals. • The larger the responses in BMD to therapy and the more precise the DEXA scan result, the shorter the period between testing in which clinically relevant differences can be found. • Precision error rates are estimated at <1% for the anterior-posterior spine and 1% to 2% for the hip. • The BMD change after the initiation of treatment must escape the precision error of the testing device or exceed the least significant change (LSC) value. • The LSC—roughly analogous to a 95% confidence interval—is 2.8 times the precision error of the test on a specific machine and site of measurement.

- If the precision error for DEXA of the femoral neck BMD is 2%, then the LSC is 5.6%.
- Changes in BMD of <2%–4% in the vertebrae and 3% to 6% at the hip could be due to inherent measurement error.

3. A clinician must also understand the anticipated response to the prescribed therapy.
   - It is not clinically useful to retest BMD before therapy would have time to affect bone turnover.
   - Alendronate and risedronate increase lumbar spine BMD by 5% to 7% and hip BMD by 3% to 6% when used for approximately 3 years.
   - These increases in BMD are associated with 30% to 50% reductions in vertebral and hip fractures.
   - Alendronate continues to increase BMD: After 10 years of treatment, it increased BMD by 13.7% in the lumbar spine, 6.7% in the total hip, and 5.4% in the femoral neck.
4. Frequent testing, as seen in bisphosphonate clinical trials, demonstrates the phenomenon of regression to the mean
   - One analysis of the FIT trial, which compared alendronate with placebo in postmenopausal women with low BMD and at least 1 vertebral fracture, focused on the early evaluation of BMD.
   - The study found a high degree of variability in BMD when tested after 1 year of treatment.
   - This wide variation in response in the first year normalized in the second year.
   - A second analysis showed that when women were divided into 8 groups, the group with the greatest increase in BMD in the first year (10.4%) also had the greatest decrease (1.0%) in year 2.
   - In addition, the group with the greatest decrease in year 1 (6.6%) had the greatest increase in year 2 (4.8%).
   - The variability in response among the 8 groups was approximately 17% (+10.4% and –6.6%) in year 1 and narrowed to a 6% difference in year 2.
   - This regression to the mean leads to a normalization of bone density results.
   - This patient variability in BMD response to the prescribed therapy should be considered when deciding to retest.
5. In summary, limitations in DEXA precision mean any changes in BMD of less than 5.6% at the femoral neck may be due to measurement error, and BMD response to bisphosphonates vacillates in the first few years of use, but can be expected to increase femoral neck BMD 3% to 6% over 3 years.
   - Therefore, if serial DEXA scanning is preformed on patients prescribed bisphosphonate therapy, it should be considered no earlier than 2 to 3 years after therapy begins.
   - When monitoring osteoporosis therapy, a BMD change within the LSC should be interpreted as “no change” and should not lead to changes in patient management.
   - If the BMD has decreased beyond the LSC there is cause for concern, and reevaluation of diagnosis and treatment are warranted.

Recommendations from Others

1. Guidelines on monitoring the clinical response to osteoporosis therapy with DEXA are available from numerous groups (Table)
   - In clinical practice, it is common for a BMD difference of 3% to 5% at the spine or 4% to 6% at the hip to be considered clinically significant.

Clinical Commentary

If follow-up is needed, rescan in 2 to 3 years. Rates of vertebral and hip fractures are significantly reduced by alendronate and risedronate, making them important in the prevention and treatment of osteoporosis. Despite controversies over the timing and necessity of monitoring bisphosphonate therapy with DEXA scans, they may be

	useful clinically if their limitations are recognized. It is necessary to wait 2 to 3 years to repeat the DEXA after initiating therapy to account for the slow rate of change in bone density and compensate for the regression-to-the-mean phenomenon seen in clinical trials. If after 2 or 3 years the bone density remains stable or has increased, reassurance can be given that fracture risk has decreased. If bone density has decreased more than the LSC, consider the following questions: Is the medicine being taken first thing in the morning on an empty stomach? Is weight-bearing exercise performed routinely, tobacco avoided, and caffeine limited? Is the patient continuing adequate calcium and vitamin D supplements? The physician should also consider secondary causes of osteoporosis, such as hyperthyroidism and hyperparathyroidism.
8. PEPID citation/access data	Koval et al. How should a DEXA scan be used to evaluate bisphosphonate therapy for osteoporosis? Available at: http://www.pepidonline.com. Last updated: January 2005. Accessed July 25, 2009.
9. PEPID content updating	1. Do you recommend that PEPID get updated on this topic? No, this topic is current, accurate, and up to date.
	2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review? No, this topic is current, accurate, and up to date.
10. Other excerpts (USPSTF; other guidelines; etc.)	National Osteoporosis Foundation, American Association of Clinical Endocrinology recommend checking DEXA within 2 years of treatment initiation.
11. Citations for other excerpts	
12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)	Most seem to recommend monitoring every 1-2 years.
SECTION 4: CONCLUSIONS	
1. Validity: How well does the study minimize sources of internal bias and maximize internal validity? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	2
2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?	
3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by “full scope” family physicians? Give one number on a scale of 1 to 7 (1=extremely well; 4=neutral; 7=extremely poorly)	1

4. If 4.3 was coded as 4, 5, 6, or 7, please provide an explanation.	
5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice? Give one number on a scale of 1 to 7 (1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)	1-2
6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.	It seems to be a change from many groups' recommendations, but it's not clear if it is a practice change in terms of what providers are actually doing. However, a recommendation to *not* monitor with follow-up DEXAs for patients being treated for osteoporosis sounds like it would be practice-changing.
7. Applicability to a Family Medical Care Setting: Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention? Give one number on a scale of 1 to 7 (1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)	1
8. If you coded 4.7 as a 4, 5, 6 or 7, please explain.	
9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit	1

implementation? Is the service, device, drug or other essentials available on the market? Give one number on a scale of 1 to 7 (1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)	
10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.	
11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient oriented? Give one number on a scale of 1 to 7 (1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)	1
12. If you coded 4.11 as a 4, 5, 6, or 7 please explain why.	The study asks indirectly whether follow-up DEXA scans are necessary by assessing predictability of response. They found that BMD rises fairly predictably, thus negating need for follow-up in their view. So although the outcome they measure is not patient-oriented (BMD), I think their finding is, as the outcome really is more the patient's need to have a follow-up scan.
13. In your opinion, is this a Pending PURL? Give one number on a scale of 1 to 7 (1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL) Criteria for a Pending PURL: • Valid: Strong internal scientific validity; the findings appears to be true. • Relevant: Relevant to the practice of family medicine • Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice. • Applicability in medical setting: • Immediacy of implementation	2

14. Comments on your response in 4.13	I think this is valid, implementable, and practice-changing.

SECTION 5: EDITORIAL DECISIONS

1. FPIN PURLs editorial decision (select one)	Pending PURL—Forward to JFP Editor
2. Follow-up issues for Pending PURL Reviewer	
3. FPIN PURLS Editor making decision	Sarah-Anne Schumann
4. Date of decision	July 30, 2009
5. Brief summary of decision	We felt this was a PURL. Secondary sources recommend routine monitoring by DEXA 1-2 years after initiation of bisphosphonate therapy, but this study indicates that treatment response is fairly predictable (in a positive direction) in BMD at 3 years. The practice recommendation would be to not do DEXA scans during the first 3 years of bisphosphonate treatment.