Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Treatment to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis – Update of a 2007 Report*

Draft review available for public comment from March 10, 2011 to April 7, 2011

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentor and Affiliation	Section	Comment	Response
Reviewer 2	Structured Abstract	I am a bit concerned about the comment in the abstract that states that "calcium is associated with a significantly increase risk of myocardial infarction" - this is based off of one recent paper from BMJ for which there has been discussion about its conclusion and methodology. I think to state it so strongly in the abstract makes it appear to be more conclusive than the topic truly is. In addition, the reference number for this article - 397 - cites I believe the wrong Bolland et al article, should be the Bolland article from BMJ 2010 not the JCEM article.	We have fixed the Bolland references. In view of the controversy over the findings, we have deleted reference to this finding from the abstract and revised the findings sections.
Chapell, Richard	Structured Abstract	To summarize a large and complex document in a single page is a difficult, if not impossible task. Without the space to define terms and add nuance to generalizations, the structured abstract may be uninformative or even misleading. For this reason we suggest that the structured abstract be removed from the document in favor of the executive summary.	We appreciate this feedback on the report format; however, it is AHRQ policy to include a brief abstract.
Chapell, Richard	Structured Abstract	The statement that ibandronate reduces risk of nonvertebral fractures leaves out the fact that evidence does not support reduction in risk for hip fractures by this agent. The product is not approved for hip fracture reduction in the United States. Moreover, the structured abstract does not specifically discuss hip fracture at all, despite this being the most important type of non-vertebral fracture, with the most debilitating outcomes. Hip fractures in the elderly are associated with a 30% one-year mortality.	We thank the reviewer for pointing this out. We have added text to the abstract regarding this point, beginning the Results section with the statement, "Alendronate, risedronate, zoledronic acid, and denosumab prevent hip fractures among postmenopausal women with osteoporosis."
Chapell, Richard	Structured Abstract	The statement that "Among those treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate." overlooks a head to head trial in which teriparatide had slightly greater effects than alendronate to reduce vertebral fractures among these patients.	We have added text regarding this study to the response to the questions on overall effectiveness and effectiveness in subgroups

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Forteo	Structured Abstract and throughout report	The following statement is included in the draft review: "Among those treated with glucocorticoids, fracture risk reduction was demonstrated for risedronate and alendronate. Few studies have compared treatments head-to-head." Yet, the fracture outcomes from a teriparatide versus alendronate active comparator trial studying the effects of these drugs as treatments for glucocorticoid-induced osteoporosis are shown in Table 38 (page 101). The statement on page 93 that the odds of vertebral fracture were similar between the groups is incorrect. Review of Table 38 on page 101 of the shows there were significantly fewer vertebral fractures in the teriparatide versus alendronate group, and no between-group difference in nonvertebral fracture	The statement regarding there being few head-to-head trials actually was intended to refer to comparisons of all osteoporosis therapies. We revised the abstract to reflect this point. The fact that there exists one head-to-head trial in glucocorticoid users does not negate our statement that few studies have compared treatments head-to-head. We have added text to clarify the findings of that study: that the odds of non-vertebral fracture were similar, and that the odds of vertebral fracture were higher with alenronate that with teriparatide.
Chapell, Richard	Structured Abstract	The statement that adherence to therapy with bisphosphonates is poor is misleading because it fails to acknowledge that adherence to treatment for any chronic, asymptomatic illness, such as hyperlipidemia or hypertension, is equally poor. Please revise.	Revised wording accordingly.
Chapell, Richard	Structured Abstract	The statement "Decreased adherence to bisphosphonates is associated with an increased risk of fracture." is misleading. Decreased adherence is associated with less risk reduction compared with more adherent patients.	Revised wording accordingly.
Chapell, Richard	Structured Abstract	"Mild cardiac events" and "established osteoporosis" are both undefined and open to a variety of interpretations.	The term "mild cardiac events" with respect to raloxifene was omitted in favor of the more accurate, "vasomotor flushing." "Established" was revised to "a diagnosis of," according to NOF guidelines or at least a stated diagnostic criterion

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Forteo	Structured Abstract, Executive Summary and throughout the report	The 2007 report and this new update incorrectly include a finding of an increase in mild cardiac events associated with raloxifene, based on 4 studies. However, these studies did not show an increase in mild cardiac events with raloxifene. The 2007 analysis leading to this incorrect conclusion classified vasodilation events for raloxifene as "mild cardiac events" (Eli Lilly Letter to Editor, Annals of Internal Medicine June 2008). Vasodilation events are hot flashes, and raloxifene is known to increase the risk of hot flashes. The relatively small trials selected for the previous systematic review and the current draft update do not include randomized, placebo-controlled trials, such as the Multiple Outcomes of Raloxifene Evaluation [MORE, N=7705] (Ettinger et al., 1999 MORE) and the Raloxifene Use for the Heart [RUTH, N=10,101] (Barrett-Connor et al, 2006 raloxifene) trials. These large trials also did not detect an increase of mild cardiac events with raloxifene. The finding of an increase in mild cardiac events associated with raloxifene is incorrect and should be removed from the update.	We have substituted the term "vasomotor flushing" and repooled the data as the one term accounts for all observations in this category. We inadvertently omitted the MORE study from the analysis of hot flashes; however, it would have simply strengthened the observed increase in risk. (and the strength of evidence was already high - we had originally rated it as moderate and neglected to change it to high in the summary table when we added new studies). The RUTH study did not report on the incidence of hot flashes.
Warner Chilcott	Executive Summary and Chapter 1: Background	Please consider updating the prevalence of osteoporosis or low bone mass in the US from 44 million people (2002 estimate) to 52 million people (2010 estimate) (NOF 2002).	We updated the prevalence
Warner Chilcott	Executive Summary and Chapter 1: Background	Estimates of the economic burden of osteoporosis provide valuable perspective and might be amplified with details on the relative contribution of different types of fractures. In particular, the economic burden of non-vertebral fractures (73% of U.S. fractures and 94% of costs) is important to Medicare Advantage plans and other payers who carry the risk for hospital and long-term care costs.	We were unable to identify data recent enough to warrant including in the report.
NOF	Executive Summary and Introduction: Background	Diagnosis and Risk Factors: NOF appreciates AHRQ recognizing its guidelines on the prevention and treatment of osteoporosis and the use of FRAX to assist in selecting candidates for treatment.	No comment needed.

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Forteo	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	Page ES-1 the diagnostics and risk factors section would benefit by focusing on who should be considered for treatment, according to the National Osteoporosis Foundation Clinician's Guide (Who Should Be considered for Treatment?) Postmenopausal women and men age 50 and older presenting with the following should be considered for treatment: - A hip or vertebral (clinical or morphometric) fracture -T-score <= -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes -Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture >= 3% or a 10-year probability of a major osteoporosis-related fracture >= 20% based on the US-adapted WHO algorithm (Reference: National Osteoporosis Foundation Clinician's Guide: http://www.nof.org/professionals/clinical-guidelines. Accessed March 23, 2011)	We added NOF guidelines to the introduction as background
Chapell, Richard	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	We believe that there is not general agreement that one can draw a line using a T-score to conclude that everyone with a BMD greater than -2.5 is not osteoporotic. When alendronate was approved the method described in product labeling for identifying patients with osteoporosis was either a BMD t-score less than -2 or a prior osteoporotic fracture (like spine or hip fracture). Moreover, the drug was shown to reduce the risk of both spine and hip fractures in postmenopausal osteoporotic women chosen using this criterion - including women with no prior vertebral fractures but a hip neck BMD below -2.0. Please rephrase the discussion of T-score to cite the source of the -2.5 definition and acknowledge that other definitions exist. Similarly, on page ES2, a T-score of -1 or greater is defined as normal. In practice, a t-score greater than -2 is generally considered "normal," as about 15 % of young women have a BMD t-score between -1 and -2 and would be considered "abnormal" if a t-score of -1 were used as lower limit of normal.	We have added the citations for the source of the -2.5 definition. Regarding the definition of "normal," the focus of this report is comparative efficacy of osteoporosis therapy, with special attention to the 5 key questions. We do not want to confuse readers with multiple definitions of densitometric criteria for the diagnosis of osteoporosis. Therefore, we have cited the source for the definition that was designated by the World Health Organization consensus panel and is used by the International Society for Clinical Densitometry, the National Osteoporosis Foundation, and multiple other guidelines. We also note that on page ES-2, we were careful to differentiate that Z-scores are preferred as the basis for the diagnosis of low bone density in premenopausal women and younger men.
Chapell, Richard	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	Z scores are described as being used for osteoporotic women and men over age 50. Z scores are intended for all adults, and can be normalized for racial background as well as age and sex. Please expand your discussion to include these facts.	The text was corrected

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Chapell, Richard	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	Please add risk of falls to the list of risk factors for osteoporotic fracture. Unlike many of the other risk factors, it is relatively independent from risk due to osteoporosis (low bone strength).	We added falling
Chapell, Richard	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	Third paragraph, first sentence: Please change "osteoporotic risk" to "osteoporotic fracture risk".	We revised as suggested
Chapell, Richard	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	Third paragraph, 4th sentence: redundant use of the phrase "10-year risk". Please remove the phrase "…and the 10-year risk of hip fracture."	We revised as suggested
Chapell, Richard	Executive Summary and Introduction: Background (Diagnosis and Risk Factors)	Final full sentence contains misplaced parentheses. Also, the use of anatomical jargon is out of place with the style of the rest of the text. Many readers will be unfamiliar with this vocabulary. Please define terms or simplify. Please devote a consistent level of detail to the description of the mechanism of action of each treatment form.	The typographical error was fixed. We also revised the discussion regarding the mechanism of action however a detailed discussion is beyond the scope of this report.
Warner Chilcott	Executive Summary and Introduction: Background	The introduction to the draft report correctly mentions complicated dosing instructions as an obstacle to compliance and persistence (p. ES-2, p. 3), and the section on factors affecting compliance notes that compliance with dosing instructions worsens with age… We propose that the complicated dosing regimen for bisphosphonates be added to the 5 barriers to compliance that AHRQ cites in its conclusions. Non-compliance to the oral bisphosphonates' dosing regimens reduces absorption and can lead to higher fracture rates…	We believe it is important to differentiate the "most commonly discussed/studied" potential barriers vs. those barriers that actually exist. Dosing instructions has not frequently been assessed as a barrier and therefore it should not be included on any list - since we are listing those barriers that are examined in the literature. Although non-compliance to dosing instructions may complicate use of the medication, that is not the conclusion in published literature (mainly because many of the adherence studies use pharmacy claims and admin data in which one cannot address compliance with dose instructions. We have elected to omit that phrase on dosing instructions in the executive summary and the intro
Peer Reviewer 6	Executive Summary	Delete (	Fixed as suggested.
Amgen	Executive Summary and Introduction	In the Executive Summary on page ES-3 and on page 3, the FDA-approval date for denosumab is given as "…May 2010". Denosumab was approved by the FDA on June 1, 2010.	Corrected

Commentor and Affiliation	Section	Comment	Response
Chapell, Richard	Executive Summary and Introduction	Discussion of the history of treatments for preventing osteoporotic fracture omits the FDA "Draft" guidance document of 1985. This document noted the importance of animal safety testing to determine whether a drug increased bone mass and produced bone that was normal (e.g., no qualitative abnormalities). For drugs like etidronate and sodium fluoride that could produce abnormal bone (osteomalacia) fracture studies were required. BMD with dual-energy gamma technology was also noted to be useful for BMD assessment. Please add this information to the discussion.	We have added a reference to the changes of note in the 1984 Guidance; however, our understanding from the Colman review is that the issue of bone biopsy to test for bone quality was not addressed until the '94 Guidance Document, as we describe.
Chapell, Richard	Executive Summary and Introduction	The 1994 document also extended the required length of clinical osteoporosis treatment studies to 3 years (from 2 years). Roles of DXA and novel biochemical markers of bone turnover were recognized for phase I and II studies.	Text revised as suggested.
Chapell, Richard	Executive Summary and Introduction	Estrogen was approved for the prevention of osteoporosis, not for its treatment. Its exemption from the requirement for demonstration of fracture reduction is based on this fact and on the fact that estrogen products were first approved for use in the menopause before the FDA guidelines were developed. Estrogen was administered in order to replace estrogen production that was reduced following menopause. This contrasts with SERMs, which were approved for treatment of osteoporosis, and thus required fracture data. Please reword the description of these agents to make this distinction.	Text revised as suggested.
Chapell, Richard	Executive Summary and Introduction	Please note that while approval for new dosage forms of agents do not require additional fracture data, approval for new indications, such as GIOP, do require fracture data.	Text revised as suggested.
Chapell, Richard	Executive Summary and Introduction	"…etidronate increased the risk for esophageal ulcerations and gastrointestinal perforations, ulcerations, and bleeding." We find no mention of this elsewhere in the document. Please ensure that the statement is justified.	This statement refers to findings in the original (2007) report.
Chapell, Richard	Executive Summary and Introduction	"…observational studies tended to report poor adherence with bisphosphonates and calcium." This phrasing implies that adherence is higher with other agents. If this is not the case, please rephrase to acknowledge the lack of evidence for other agents. Also, please state that poor adherence is characteristic of chronic, asymptomatic illnesses and not a unique property of this population.	The studies on adherence to treatments for OP are limited almost exclusively to bisphosphonates (alendronate) and calcium. However, we have clarified the text to indicate that adherence to BPs is not low compared to that with other agents or chronic conditions.

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Chapell, Richard	Executive Summary and Introduction	Final paragraph: The name of the new biological agent should be provided in brackets (Denosumab).	Revised as requested
Chapell, Richard	Executive Summary and Introduction	Mention of lasifoxifene is unnecessary, as it is not marketed in the United States and not discussed in the current review. Please remove. Similarly, mention of pamidronate is unnecessary as it is not approved for treatment of osteoporosis and is excluded from the report.	Deleted as suggested
Amgen	Executive Summary and Introduction-KQ 1	In the Executive Summary on page ES-6 and within Scope and Key Questions on page 6, denosumab is described as a "once-a-year injection." The approved Prolia® dosing schedule is an every-6-month injection. Thus, Amgen requests the description be modified to: "the monoclonal antibody, denosumab (Prolia®; Amgen; every-6-month injection)". Similarly, in Table 1 on page 11, Amgen requests changing the description of the denosumab dosing schedule from "…twice yearly" to "…every 6 months".	Revised as requested
Chapell, Richard	Executive Summary and Introduction -KQ 1	Boniva is injected four times a year, not twelve as stated here. Similarly, denosumab is injected every six months, not once a year.	The dosing schedule description was changed as requested.
Amgen	Executive Summary and Introduction -KQ 1	In the Executive Summary on page ES-6 and on page 6, Amgen requests that the company name be spelled as "Amgen" rather than "AmGen."	The spelling of Amgen was corrected as requested

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Novartis	Executive Summary and Introduction -KQ 4	This review contains reports of adverse events of osteonecrosis of the jaw (ONJ) that were reported with Zometa (zoledronic acid) injection which is not indicated for osteoporosis… Therefore, in the Executive Summary section (ES-17) and the Conclusion section (ES-22), and in Chapter 3 (Pages 131 and 135) under the heading Osteonecrosis of the Jaw, we recommend that it clearly state that the use of zoledronic acid was for oncology purposes in these reports. For example, the third sentence under Osteonecrosis of the Jaw on page ES-17 should be slightly modified for clarity: “However, a large recent case series that reviewed 2408 cases of osteonecrosis of the jaw to assess the possible association between use of bisphosphonates and osteonecrosis found that 88 percent were associated with intravenous bisphosphonate therapy for oncology indications. Only ten percent of reports were associated with oral and IV bisphosphonates for the prevention or treatment of osteoporosis.”	The text was revised accordingly to specify that ONJ was reported in patients being treated for malignancies.
Peer Reviewer 6	Executive Summary and Introduction -KQ 1	no oral exists, only iv	We removed the reference to an oral preparation.
Chapell, Richard	Executive Summary and Introduction -KQ 1	Zolendronate is described as "oral and IV". To the best of our knowledge, no oral form is available.	We removed reference to an oral form.
Novartis	Executive Summary and Introduction -KQ 1	On page ES-7 under Key Question 1, there is a reference to an oral form of zoledronic acid and the brand name “Zometa”. Response: These should both be removed since there is no oral form of zoledronic acid and Zometa is used for oncology purposes only.	We removed reference to an oral form and changed "Zometa" to "Reclast."

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APTA	Executive Summary and Introduction -KQ 1	APTA encourages AHRQ to recognize the multifactorial nature of the interventions necessary for prevention of fractures in the low bone density or osteoporosis patient populations. Key question 1 indicates that benefits should be studied into "exercise in comparison to above agents." APTA suggests that this is too narrow. Exercise and physical activity should not be viewed purely as an alternative to the other modalities and agents, but rather also in a supplemental role. Further investigation should be pursued to identify the benefits of a multifactorial, combined treatment approach versus individual treatments in isolation of one another. A 2006 review article published in the American Journal of Medicine advocated for a pyramidal approach for preventing osteoporosis-related fractures. The first level of which called for the use of dietary supplements and physical activity/falls prevention, with the second tier focused on addressing the causes of osteoporosis, and the third tier investigating pharmacology.1 The 2010 clinical practice guidelines for the diagnosis and management of osteoporosis from Canada also advocates for an "integrated approach	In addition to the meta-analysis included in the draft report, we have identified only one exercise trial that satisfied the inclusion criteria of the report. We have added a description of its findings to the response to Key Question 1; however, the study was not powered to detect difference in fracture rate.
Amgen	Executive Summary-Analytic Framework-Figure S-1; Figure 1	Amgen requests that denosumab be added to the interventions listed in Box 1. This box lists the interventions reviewed for Key Question 1, and denosumab was one of the agents reviewed	Denosumab has been added to Figure S-1 and Figure 1.
Chapell, Richard	Executive Summary-Bullet points for KQ 1	Bullet points are inconsistent regarding the strength of evidence supporting them. Wile some correctly state that there is Good or Moderate evidence, others use imprecise terms like "a large body of literature". This tells us nothing about the quality or consistency of the evidence. Please use consistent terminology, and report the strength of evidence for each conclusion.	Each bullet point now has a strength-of-evidence rating consistent with GRADE.

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Novartis	Executive Summary-Bullet points for KQ 2	On page ES-15, under Key Question 2, the following statement is misleading: One RCT found no influence of age on the effect of zoledronic acid in lowering the risk for vertebral or non-vertebral fractures but found that only women under 75 experienced a benefit in reduced risk of hip fracture. However, another RCT found that age influences the effect of zoledronic acid on vertebral fracture risk but not the risk of non-vertebral or hip fracture. Response: The statement that only women less than 75 years experienced reduction in hip fracture rates with zoledronic acid is misleading. It is important to note that this subgroup analysis was not statistically powered. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial was powered to evaluate hip fracture rates in all randomized patients and Reclast demonstrated a significant relative risk reduction in hip fractures of 41% (p=0.002) over 3 years. This information is in the current Reclast package insert.	We have verified that the results of the text summarizing the analysis of zoledronic acid by age on page ES-16 correctly portrays the results of the referenced studies. However, we have added the caveat that the subgroup analysis by age was not powered to show a difference in hip fracture rates.
Forteo	Executive Summary -Bullet number 8 (KQ 2)	Page ES-15 bullet 8 is not aligned with page 111. The information should be aligned by updating the statement “One RCT found no effect of age on the influence of teriparatide on vertebral fracture but found an effect on the risk of non-vertebral fracture.” to “The relative effect on teriparatide on reducing the incidence of new vertebral fractures and nonvertebral fragility fractures was statistically indistinguishable in younger and older patients. Treatment by age interaction was not statistically significant by a subset analysis of the randomized controlled trial.	In a further revision, we have adopted the wording suggested by the reviewer.

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Forteo	Executive Summary -Bullet number 11 (KQ 2)	Page ES-15 bullet 11 describes information concerning the effects of some drugs by baseline renal function. We suggest that additional relevant published information be included in the document concerning the effects of teriparatide by baseline renal function (Miller et al. '07)?. The paper describes a post-hoc analysis from the Fracture Prevention Trial, a phase 3 randomized, double-blind, placebo-controlled trial of teriparatide in postmenopausal women with osteoporosis at high risk for fracture. Compared with placebo, teriparatide significantly increased bone formation marker PINP and lumbar spine and femoral neck BMD within each renal function subgroup, and there was no evidence that these increases were altered by renal insufficiency (each treatment by- subgroup interaction p>0.05). Similarly, teriparatide mediated vertebral and nonvertebral fracture risk reductions were similar and did not differ significantly between patients with normal or impaired renal function (treatment-by subgroup interactions p>0.05). No particular safety issues were identified in subgroups defined by renal function. (Reference: Miller PD, Schwartz EN, Chen P, et al. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. Osteoporosis Int. 2007; 18(1):59-68)	We inadvertently excluded this study from the report. We have added this information to the bullet and also to the main text of the report (page 113).
Peer Reviewer 1	Executive Summary, Tables A and 56 (KQ 3), KQ 3, Conclusion	"Moderate strength: a meta-analysis and ten out of eleven observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture (vertebral, non-vertebral or both)." **Comment:** While I agree that this is not an unreasonable statement, the report need to consider the "confounding by healthy adherer" effect	We have now addressed the healthy adherer effect in the discussion of the adherence results.
Novartis	Executive Summary and Chapter 3	On page ES-17 and in Chapter 3, page 132, there is an Atrial Fibrillation (AF) section which is summarized on page ES-22 and in Chapter 3 page 158 under Table A. Summary of Evidence (number 4). These sections describe a moderate risk of AF with zoledronic acid under Strength of Evidence. Response: We request that all references to the risk of atrial fibrillation with zoledronic acid be removed based on reviews and publicly issued statements from the FDA in 2007 and 2008. Please see a detailed overview of these statements and their findings below [see separate file].	We have identified additional studies that we now describe. In addition, we cite the two FDA statements requesting additional evidence. We have downgraded the level of evidence but retain the conclusion because of interest in the topic and the FDA's continued concern

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Peer Reviewer 6	Executive Summary	It is unclear what is meant by mild cardiovascular events from a clinical perspective	We have changed the term to the correct, "vasomotor flushing" and hot flashes, specifically.
Chapell, Richard	Executive Summary	In the discussion of atypical fractures of the femur, it is implied that the pooled analysis of three trials "identified an increase in the risk" for atypical fractures. First, these were case series and not trials. While the EPC may have concluded that risk estimates were elevated, differences were tiny and confidence intervals wide. Moreover, there is a large body of epidemiologic data (See Shane et al.; reference 135) that do not indicate increased risk, that do not appear to have been considered. We do not believe that this analysis should be cited as evidence for increased risk. While the body of the review (page 135) makes this somewhat more clear, we request that the bullet point in the Executive Summary be rewritten to state that when viewed in its entirety, the evidence supporting an incre…{stopped due to word limit}	We have added narrative reviews of all existing evidence and have revised the conclusion accordingly: "Limited data from clinical trials and observational studies support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent, nevertheless these data were sufficient for FDA to issue a Warning regarding this possible adverse event."
Peer Reviewer 6	Executive Summary	In FLEX, 5 years off was compared with 10 years on; those with 5 on, 5 off had a higher risk of clinical vert fxs at 10 yrs on. If this is the study to which you refer here, the conclusion you state seems confusing	We have revised the sentence to read as follows: "One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and non-vertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued."
Peer Reviewer 1	Executive Summary and Conclusions: Table A and Table 57 and other tables	"high" and "strong" are both used for level of evidence in at least one of the tables; this needs to be cleaned up.	"High" is the approved term: we have revised accordingly here and throughout the report.
Peer Reviewer 6	Executive Summary and Conclusions: Table A (KQ 1) and Table 57 (KQ 1)	non-vertebral	We have made the change
Amgen	Executive Summary and Conclusions: Tables A, KQ 1 and Table 57 (KQ 1)	“Denosumab reduces the risk of vertebral, no-vertebral and hip fractures in postmenopausal women with osteoporosis.” Amgen requests changing “no-vertebral” to “non-vertebral” for accuracy.	We have made the change

Commentor and Affiliation	Section	Comment	Response
Amgen	Executive Summary and Conclusions: Tables A, KQ 1 and Table 57	In the Summary of Evidence tables (Table A on page ES-20 and Table 56 on page 155), denosumab is shown to have a "high" strength of evidence for reducing the risk of fractures, including vertebral fractures, in postmenopausal women with osteoporosis. Therefore, in the Executive Summary under the section What We Know About Whom to Treat and How on page ES-24 and in the Discussion on page 162, Amgen requests that denosumab be included in the list of agents that have strong evidence supporting use for reducing vertebral fractures, that is: "For reduction in vertebral fracture risk, there is strong evidence supporting the use of bisphosphonates, raloxifene, teriparatide, and denosumab". This addition would be consistent with other sections of the Draft Report where the authors conclude that denosumab reduces the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis (for example, in the Structured Abstract on page viii; in the Conclusions on pages ES-13 and ES-14; within Key Question 1 on page 28).	We have made that change.
Amgen	Executive Summary and Conclusions: Tables A and 57 (KQ 2)	"Alendronate, etidronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis." In this statement, the group "postmenopausal women with osteoporosis" is included as a high-risk category. Denosumab is not included in this list, which Amgen believes to be an oversight… Amgen requests that denosumab be added to this summary statement for postmenopausal women with osteoporosis. For example, the report may state, "alendronate, etidronate, ibandronate, risedronate, teriparatide, raloxifene, and denosumab reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis."	We have made that change.
Novartis	Executive Summary and Conclusions: Tables A and 57 (KQ 2)	On page ES-20, under Table A. Summary of Evidence (number 2), zoledronic acid is clearly missing from the list of bisphosphonates. Response: Zoledronic acid needs to be added to this section to read as follows: "Zoledronic acid, alendronate, ibandronate, risedronate, teriparatide, and raloxifene reduce the risk of fractures among high risk groups including postmenopausal women with osteoporosis"	We have made that change.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 6	Executive Summary and Conclusions: Table A and 57 (KQ 2)	What about teriparatide?	Based on a new RCT, we have added Teriparatide to the conclusion about drugs that effectively prevent fracture in patients taking glucocorticoids.
Amgen	Executive Summary and Conclusions: Table A and 57 (KQ 3)	Table A, Key Question 3, on page ES-21 provides reported rates of adherence in randomized controlled studies evaluating bisphosphonates or raloxifene… these data [on denosumab] have not been included as evidence for this adherence question (Brown 2009, Kendler, 2010)… Amgen requests that this report be complete in its description of the evidence for adherence and compliance data from randomized controlled trials by including these data for denosumab. Additionally, Amgen requests the addition of statements about denosumab adherence in randomized controlled trials in Question 3a, page 114 and Table 49, page 119, and that Table 56, page 157 be updated to be consistent with the requested changes made to Table A.	We have re-reviewed studies that assessed adherence to denosumab; we have added the adherence data to Table 49 and an entry into the Conclusions table.
Peer Reviewer 1	Executive Summary and Conclusions: Tables A and 57 (KQ 4)	"Moderate strength: Zoledronic acid is associated with an increased risk of atrial fibrillation relative to placebo." **Comment:** ?Moderate? seems weak based on so few cases. I would suggest that the report re-consider the strength of the data for this potential association.	We have identified additional studies that we now describe. In addition, we cite the two FDA statements requesting additional evidence. We have downgraded the level of evidence but retain the conclusion because of interest in the topic and the FDA's continued concern
Peer Reviewer 1	Executive Summary and Conclusions: Tables A and 57 (KQ 4)	"Moderate strength: A review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphonates found that 89 percent of the cases were associated with treatment of malignancy and 88 percent of cases involved intravenous therapy, previously zoledronic acid." **Comment:** The report describes this as moderate strength, but it does not clarify what is of moderate strength, an association between what and what? It would be more useful if the report reviewed the observational data.	We have added all subsequent observational studies and have clarified the conclusion as follows: One trial, one post-hoc analysis of three trials, two large observational studies, and a review of 2,408 cases of osteonecrosis of the jaw in patients taking bisphosphonates for osteoporosis prevention or treatment found that the incidence of osteonecrosis of the jaw in this group was small, ranging from less than one to 28 cases per 100,000 person-years of treatment. We classified the conclusion as moderate in strength.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 1	Executive Summary and Conclusions: Tables A and 57 (KQ 4)	"Atypical fractures: "Limited data from clinical trials and observational studies support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent, nevertheless these data were sufficient for FDA to issue a Warning regarding this possible adverse event." **Comment:** Please include all of the recent observational data on this topic and attempt a more definitive statement. the preponderance of data give moderate support for an association with long-term BIS use and atypical fracture. the risk is very low (approx 1 per 1,000 PYs) and appears much smaller than the risk reduction associated with BIS use in the first five years. however, after five years, this benefit-risk of BIS may reverse.	We have added the most recent observational studies as well as the ASBMR statement and have revised the conclusion to read as follows: Limited data from clinical trials and observational studies support a possible association between bisphosphonate use and atypical subtrochanteric fractures of the femur. Data are not consistent, nevertheless these data were sufficient for FDA to issue a Warning regarding this possible adverse event."
Peer Reviewer 1	Executive Summary and Conclusions: Tables A and 57 (KQ 4)	"There is a signal from observational studies that use of an oral bisphosphonate is associated with an increased risk of esophageal cancer." **Comment:** I believe that there was one case series from the FDA (I don't consider a case series a "study" since there is no denominator and no comparator) and one UK study that suggests an increased risk. I would describe this as ONE study and one case series. I might be splitting hairs but, as an epidemiologist, I think this is an important distinction.	Additional studies were added and the conclusion was revised to reflect the lack of evidence
Peer Reviewer 6	Executive Summary and Conclusions: Tables A and 57 (KQ 4)	this-again-implies higher risk of clin vert fx with 10 years of alendronate vs. 5 on, 5 off, when the outcome was the reverse-fewer clin verts with 10 year rx of 5 on, 5 off	We have rephrased the text to read as follows: "One large RCT showed that after 5 years of initial alendronate therapy, vertebral fracture risk and non-vertebral fracture risk were lower if alendronate was continued for an additional 5 years instead of discontinued."
Peer Reviewer 6	Executive Summary and Conclusions: Tables A and 57 (KQ 4)	T score; the non-verts were reduced in the 10 on group compared with 5 on, 5 off-this needs to be stated more clearly, I think	We have rephrased the text as follows: A post hoc analysis of this same trial reported that there were statistically significant non- vertebral fracture risk reductions for women who at baseline had no vertebral fracture but had a BMD + score of -2.5 or less."

Commentor and Affiliation	Section	Comment	Response
Amgen	Executive Summary and Conclusions: Tables A and 57 (KQ 5a)	"changes in BMD during therapy are associated with a minority of antifracture efficacy; even patients who continue to lose BMD during therapy have had statistically significant benefits in fracture reduction." While there are published data that support an antifracture benefit in subjects who lose BMD on therapy, Amgen believes that the literature review to address this question was incomplete. Generally, the fracture risk reduction benefits for patients who lose BMD on therapy are in comparison to patients receiving placebo(Chapurlat 2005). In the FIT study, subjects randomized to alendronate had a new vertebral fracture at twice the rate if their BMD declined or stayed the same compared with those with gains in BMD of ≥ 3% (Hochberg 1999). Additionally, an analysis of data from three pivotal risedronate fracture end point trials showed that risedronate-treated patients whose BMD decreased were at a significantly increased risk of vertebral fracture as compared with those whose BMD increased (Watts 2004). Based on this additional evidence and for completeness, Amgen requests stating that although patients benefit from therapy compared with placebo regardless of changes in BMD, evidence suggests that subjects who lose BMD while on therapy have a greater fracture risk than those subjects who gain BMD.	Our statements and the supporting citations are correct, and the literature cited complete. While some studies suggest that greater change in BMD in active therapy groups predicts greater anti-fracture efficacy, these changes have not been established to apply to individuals under active therapy. Nor is there clinical information to guide appropriate responses to declines in BMD under active therapy such as increasing medication dose, or the influence of discontinuing therapy among individuals who experience declines in BMD under active therapy but may nonetheless derive fracture protection. As a result, we would not favor inserting the suggested statement until such evidence is available, for fear that clinicians will interpret that statement as supporting the discontinuation of potentially beneficial medication as a result of loss of BMD under active therapy. Such a recommendation is premature without adequate existing research to support it. We have added this distinction between groups and individuals to the text.
Peer Reviewer 1	Executive Summary: What we know about whom we treat and how	This section is very useful. I have not noticed this in other AHRQ evidence reports.	This is helpful feedback. No response needed.
Peer Reviewer 1	Executive Summary: What we know about whom we treat and how; Discussion	"Post hoc analyses of open-label extension data support the thesis that certain features predict continued fracture reduction with a 10-year instead of 5-year duration of alendronate therapy: BMD T-score of -1 to -2 (if women have baseline fractures), and BMD T-score <-2 if women do not have baseline fractures. It is unknown if these same precepts will hold with other osteoporosis pharmacotherapies. Studies have not directly compared the antifracture effects of longer durations of therapy." **Comment:** There is such scant data here. While I agree that this is a very important area, I would have not made specific comments because of the lack of substantial data.	While we agree that the evidence is scant regarding this issue, we feel that is all the more reason to include these statements. It is tremendously important that clinicians be aware of the paucity of studies specifically designed to assess long-term anti-fracture efficacy.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 1	Executive Summary: What we know about whom we treat and how	"There are no controlled trial data regarding anti-fracture efficacy of pharmacotherapy for idiopathic osteoporosis in men, so the comparative efficacy of available treatments has not been assessed among men with idiopathic osteoporosis" **Comment:** Is this really true??? Wow.	We have changed the text to read "To date, the comparative efficacy of available treatments has not been assessed among men with idiopathic osteoporosis."
Peer Reviewer 1	Executive Summary: What we know about whom we treat and how; Discussion	"With the advent of tools such as the WHO FRAX, selection of treatment candidates will likely be refined. Emerging research is judging the antifracture effects of medications according to level of baseline FRAX score" **Comment**: I agree with this statement. however, there are almost no data supporting FRAX as a guide for treatment. FRAX can "suggest" treatment based on non BMD risk factors, for which anti-resorptive treatment will not modify. a recent observational study from SOF pointed this out. the report should point out this weakness of FRAX very clearly. FRAX is a good tool for risk stratification. But, at this point, it is not an evidence based tool for pharmacologic treatment decision making. I believe that most expert clinicians use it as a communication tool, i.e., helping to convince women that they don't need treatment.	To reflect this point, we have modified the text as follows "...according to level of multivariable risk prediction instruments."
Peer Reviewer 1	Executive Summary: Remaining Issues; Future Research	Well done. However, I might suggest one minor edit {referring to this paragraph}:"One way forward is to move away from BMD-based measures of risk and conduct trials that use a risk assessment-based method of identifying patients, such as the FRAX. Such risk assessment methods can incorporate other variables known to be associated with risk of fracture that go beyond bone mineral density." **Comment:** This is a very important statement. I might suggest that it be broadened to also include re-analysis of existing trials, assessing whether application of FRAX estimates post-hoc allows for identification of subgroups of subjects at higher or lower risk than the typical subjects.	We have added the following text to the Future Research Section: "Re-analysis of existing trials should assess whether application of FRAX estimates post-hoc allows for identification of subgroups of subjects at higher or lower risk than the typical subjects."
Peer Reviewer 6	Executive Summary	Whom?	We changed "who" to "whom."
Peer Reviewer 1	Introduction: Chapter 1	Excellent	No response needed.
Peer Reviewer 2	Introduction: Chapter 1	Seems reasonable, appreciate overview of FDA approval process	No response needed.
Peer Reviewer 4	Introduction: Chapter 1	Ok	No response needed.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Introduction: Chapter 1	Concise with enough background information.	No response needed.
Peer Reviewer 3	Introduction: Chapter 1	Introduction is well done. Osteoporosis is well defined. Below at line 33, the clinical diagnosis of osteoporosis is based on bone mineral density testing. That is not always so. A patient who presents with one or more fragility fractures can be diagnosed by ruling out other causes. This should probably read "the clinical diagnosis may be based on bone mineral density measurements".	Wording was revised as suggested
Warner Chilcott	Introduction: Chapter 1	Atelvia, different from the other oral bisphosphonates, was specifically designed to improve the absorption of risedronate in the presence of food… To achieve this, Atelvia has a pH-sensitive enteric coating that ensures the drug releases in the small intestine at pH>5.5, and Atelvia contains a chelating agent (EDTA) to reduce the binding of risedronate to divalent cautions such as calcium. This technology might be mentioned on page 5 of Chapter 1, where new dosage forms are mentioned, eg, by inserting "including an oral bisphosphonate that should be taken immediately after breakfast" in the sentence, "… several of the bisphosphonates have become available in new, less frequently administered, forms, and a new biological agent is now available."	Drug and description were added to Table 1
Warner Chilcott	Introduction: Chapter 1- Scope and Key Questions	We propose that Atelvia be added to the list of risedronate products assessed in the report, eg, p. 7: "Risedronate (Actonel®; oral once-a-week; Atelvia™; DR oral once-a-week)" and Table 1 (p. 9).	We have added the drug and its dosing instructions to Table 1; however we identified no placebo-controlled or HTH trials testing its efficacy.
Warner Chilcott	Introduction: Chapter 1- Scope and Key Questions	We recommend deleting information regarding risedronate dosages that are no longer marketed, specifically 2.5 mg daily (p. 39, tables 6-9) and Actonel with calcium (table 1, p.9).	We have added a footnote to the relevant tables

Commentor and Affiliation	Section	Comment	Response
Amgen	Introduction: Chapter 1- Scope and Key Questions	Table 1 on page 11 states that Prolia® (denosumab) is "indicated for treatment of postmenopausal women with osteoporosis at high risk for fracture." This is a correct but abbreviated presentation of the US Food and Drug Administration (FDA)-approved indication. Amgen requests that the complete indication, as specified in the Prolia® prescribing information, be included in the report. Specifically, Prolia® is "indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, nonvertebral, and hip fractures"1. Inclusion of this full indication would provide a more complete characterization of the intended patient population.	We have added the full indication.
Peer Reviewer 1	Methods: Chapter 2	Excellent and well described	No response needed.
Peer Reviewer 2	Methods: Chapter 2	I think the search criteria are justifiable and logical	No response needed.
Peer Reviewer 4	Methods: Chapter 2	Ok	No response needed.
Peer Reviewer 3	Methods: Chapter 2	Methods are clearly outlined. This is not my area of expertise, but all of the analyses seem appropriate.	No response needed.
Peer Reviewer 7	Methods: Chapter 2	The search seems to be complete. Inclusion criteria did not address prior meta-analyses, though the results section used a lot of space to talk about them.	In the Methods section, we describe the fact that we include the results of prior published systematic reviews that included meta-analyses. For example, we say "For the third prong of our approach, we identified any relevant systematic reviews that have appeared since the original report was released and added the pooled findings of the new meta-analyses to the tables of pooled results created for the original report." And in describing included study designs for efficacy and safety, we note that we included RCTs and relevant systematic reviews.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Methods: Chapter 2	The report lacks real data synthesis. For efficacy and effectiveness, the report said OR was calculated using the Peto's method and Peto's method is a way to combine studies in a meta-analysis. However, the result section reported results from the previous meta-analyses and listed results from the newly identified RCTs. There are no results of meta-analyses conducted in this report by combining older studies and studies identified by this report. Moreover, no tests and exploration of heterogeneity, or sensitivity analyses were conducted.	We inadvertently left the description of the Peto method in our description of the analysis for efficacy; we have since deleted it.
Peer Reviewer 7	Methods: Chapter 2	It is fine to choose OR for rare event; however, the report has been using both RR and OR and in some cases, the event is not very rare. It would be consistent and clearer for the readers to use only RR. Please see the chapter of the quantitative synthesis for the CER methods manual, which has a section specifically talks about combining rare event.	We used RR in only two instances in the reporting of adverse events, once to report the results of an observational study and once to report the results of a published meta-analysis. We reported OR for all of our own analyses of adverse events as we customarily do.
Peer Reviewer 7	Methods: Chapter 2	It is a legitimate reason not to indirect comparison because of vast baseline differences between populations such as age, BMI and race/ethnicity etc.; however, the report does not provide assessment of clinical and methodological heterogeneity.	Since we didn't pool efficacy studies, we didn't analyze heterogeneity per se, however we assessed applicability according to the method of Gartlehner, which indirectly considers heterogeneity, and we report these results for each set of studies an in Appendix C.
Peer Reviewer 7	Methods: Chapter 2	To combine rare adverse events, it is not true that all asymptomic methods require corrections and some methods like M-H methods and Peto's methods don't need correction. The exact method, which is better theoretically, does not show advantages in simulation studies. Again, please see the chapter of the quantitative synthesis for the CER methods manual for more information, which has a section specifically talks about combining rare event. The chapter does not recommend the 0.5 correction factor, either.	We did not use a 0.5 correction factor for the adverse events analysis.
Peer Reviewer 7	Methods: Chapter 2	Reporting of OR as infinity does not provide useful information for the readers and the investigators could report the raw numbers. On the other hand, while adding 0.5 is not the best choice for meta-analysis, adding 0.5 has been shown to produce the best OR for individual studies with zero event in on e arm if an OR needs to be calculated for a study.	We report these confidence intervals to show the lower bounds. We did not add a 0.5 correction factor for adverse events analysis. Also, we now report the risk differences as well, for significant differences.
Peer Reviewer 7	Methods: Chapter 2	The need to include observational studies are carefully assessed based on the methods guide. How about other areas in this CER in terms of using the guide? Is Jadad score adequate for quality rating for RCTs	We provide Jadad scores as well as assessment of allocation of concealment in the evidence table for trials

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Methods: Chapter 2	OR like (Inf+, 95% CI 0.03, inf+) does not provide useful information and is confusing for the readers. The investigators should consider reporting raw data, or adding 0.5 to calculate OR for individual studies.	Please see response above.
Peer Reviewer 7	Methods: Chapter 2- Quality Assessment	For observational studies, provide summarized quality assessment based on criteria listed in page 20. For adverse event, test, and exploration (when there are enough number of studies) of heterogeneity should be conducted. Such information is of interest in itself, and also it would provide some information to evaluate the appropriateness of these meta-analyses. In addition, forest plots should be considered to present data.	We have constructed and added forest plots for all AE comparisons with 10 or more studies, and these show the tests of heterogeneity. Regarding assessing quality of observational studies of adherence, it is very difficult to devise a standardized assessment of quality and a "rating" since none exists. The Newcastle Ottawa for observational cohorts does not apply to most of the adherence studies. We tried to list those objective factors for each study that might be related to both quality and generalizablity, such as how adherence (outcome) was measured and size and location of study (generalizability). We did not apply particular scales to those studies that focused solely on adherence. We have added a discussion of this issue to the Methods section.
Peer Reviewer 7	Methods: Chapter 2	Why do the investigators make the decision to perform meta-analyses for adverse events, but not for benefits? Similar analysis should have been done for benefits, too.	The decision to do meta-analysis only on adverse events and not for effectiveness was based on discussion with the associate editor and TOO regarding the design of the original report, which relied largely on prior published meta-analyses. Since this is an update of the prior report, we added new evidence into the existing framework.
Peer Reviewer 1	Results: Chapter 3	1. Background well articulates the state of affairs and points toward the key questions 2. Scope and key questions reflect the important questions of the day 3. Methodology is sounds and rigorous	No response needed
Peer Reviewer 3	Results: Chapter 3	The results are generally clearly presented. Under each of the questions, the figures, tables, and references are quite adequate. I believe they have included all studies that are applicable that have been published since their last effort. My principle concern is over three adverse events, one related to calcium supplements, another to the development of atrial fibrillation with bisphosphonates, and third, mild cardiovascular events associated with SERMs. See below.	Each of the specific concerns is addressed in response to specific comments below and earlier. We have revised the report text accordingly.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Results: Chapter 3	The characteristics of the studies were not clearly and adequately described and there are no assessments of clinical and methodological heterogeneity.	We addressed potentially important sources of heterogeneity across studies, separately assessing results according to baseline T-score, presence vs. absence of pre-existing fracture, differences in dose and duration of treatment, etc. We also used the criteria of Gartlehner et al., to evaluated characteristics that contribute to study applicability and heterogeneity. A table of these evaluations appears in Appendix C
Peer Reviewer 6	Results: Chapter 3	Regarding raloxifene, I am very troubled by the statement that it is associated with mild cardiac events, citing 4 papers that were all relatively small - on was done entirely in Asia with Asian women - and 3 of the 4 make no reference to adverse events of chest pain. Where are the very large MORE and CORE trials? In MORE, as sub-group analysis of women with elevated cardiac risk at baseline showed a possible reduction in cardiac events with raloxifene (Barrett-Connor et al). The RUTH trial - another huge RCT - in women with established coronary disease showed neither a reduction nor a risk of cardiac events with raloxifene vs placebo. That study did show an increased risk of "fatal stroke" (MEDRA term) with raloxifene in the most severe of the women - the two quartiles with the highest baseline risk for cardiovascular events. Raloxifene does increase risk of DVT - but I think your analysis, ignoring the MORE data, is in error in attributing "mild cardiovascular events" to raloxifene. I hope you will look at this again.	We have re-reviewed all the studies that reported what were originally called "mild cardiac events" and discovered that what was being reported was, in fact, hot flashes and flushing. Thus, we have completely revised the text, including the conclusions.
Amgen	Results: Chapter 3	In pooling and interpreting the observed adverse event data from disparate clinical trials, caution should be taken in interpreting results for adverse events as “statistically significant.” In an adverse event analysis of a clinical trial, the p-value is considered more as a “descriptive statistic”, which is different from the efficacy analysis, especially since the events are not specified in advance. Amgen recommends including a statement about the limitations of pooling observational data for adverse events in this chapter or in Chapter 4: Summary and Discussion.”	This is a good point and we have added it the limitations section.
Peer Reviewer 7	Results: Chapter 3-Literature Search	It is not clear what "accepted for analysis" means - meta-analysis (not likely)? Narrative description?	We have clarified the sentence to read for "accepted for inclusion" for narrative description.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Results: Chapter 3- KQ 1	This section used a lot of space to talk about prior meta-analyses. However, there is no critical assessment of these meta-analyses, where sometimes the results did not agree. The quality of these meta-analyses could vary greatly. Also what is the real value to include all these prior-meta-analyses while some earlier meta-analyses only included, for example four studies? Is there a best meta-analyses that summarized the previous studies?	The literature on this topic-both original studies and systematic reviews- is voluminous. This report represents an update of an earlier report, for which AHRQ had determined, given budget and time constraints, and based on work by Whitlock and others, that the best method was to include the prior meta-analyses, as they responded to the questions, and not to redo these analyses to incorporate new study findings. For the update report, the volume of literature was equally large, and the TOO and AE accepted our use of prior meta-analyses. For the sake of completeness, we chose to include all prior meta-analyses, rather than trying to pick and choose what one might be the "best."
Peer Reviewer 7	Results: Chapter 3- KQ 1	As mentioned in the method section, though methods for meta-analyses was talked about, but no results on combined (pooled) analyses conducted for this report were found.	We have ensured that the Methods section clearly addresses how the efficacy data are presented and have moved the description of the quantitative synthesis to the section of the Methods chapter that describes themethods for KQ4.
Warner Chilcott	Results: Chapter 3-KQ 1	AHRQ's conclusion that differences between bisphosphonates, if any, are small, is inconsistent with health plans' analyses of their members' fracture incidence (Watts 2010 for AACE, Qaseem 2008 for ACP, Grossman 2010 for ACR)… In particular, unlike other bisphosphonates, there is no evidence from analysis of prospectively defined endpoints from randomized controlled trials (RCTs) that ibandronate treatment resulted in reduced risk of non-vertebral fractures… We recommend removing ibandronate from the list of products for which there is "good evidence" for prevention of non-vertebral fractures or "high" strength of evidence for reduction of the risk of non-vertebral fractures, including the following: second bullet of both the Executive Summary's Conclusions (p. ES-13) and Key Points on p. 28, first paragraph of the Discussion (p. 160), Table 1 (p. ES-19), and Table 56 (p. 155). Please also consider removing the following statement from Table A and Table 56: "The effect of ibandronate is unclear, since hip fracture risk reduction was not a separately reported outcome in trials reporting non-vertebral fractures."	We have deleted the statement regarding differences among bisphosphonates and have removed ibandronate from the list of agents that prevent non-vertebral fracture, but we have retained the statement regarding ibandronate and hip fracture, because it is true that hip fracture risk reduction during ibandronate use has not been studied in randomized trials.

Commentor and Affiliation	Section	Comment	Response
Warner Chilcott	Results: Chapter 3-KQ 1	Please consider adding information about the timing of onset of fracture prevention benefits. In light of patients' low persistence with oral bisphosphonate therapy, it is pertinent that ibandronate has not demonstrated fracture reduction until patients have completed 36 months of therapy (Boniva PI), whereas risedronate has achieved significant fracture reduction at six months (Actonel PI, Roux 2004, Sorenson 2003) and alendronate at 12 months (Fosamax PI)	The timing of the onset of fracture reduction was not a key question and is not within the scope of this report
Peer Reviewer 7	Results: Chapter 3-KQ 1 Key points and general	As mentioned in the comments for method section, the report lacks real data synthesis. Therefore for the Key points, there are only statements like "There is good evidence from RCTS that alendronate,…, and raloxifene prevent vertebral fractures in postmenopausal women with osteoporosis". (pg 28) However, there is no estimate of the actual effect size using all available information to help users of this CER to understand the magnitude of effectiveness of these therapeutic drugs, and calculate NNT or NNH to facilitate interpretation.	The effect sizes, usually as relative risk reduction, are included in the results for both pooled findings and for individual studies. If the comment really pertains to having a single pooled estimate for each drug and fracture type, as we indicated previously, it was not the method of this CER to produce a new single, pooled result for each drug. Particularly, when one considers data such as presented in Table 4, existing pooled risk reduction for alendronate, all values are between 0.36 and 0.55, well exceeding the "decision threshold" to treat. Also, we have revised all strength of evidence assessments to reflect GRADE wording.
Peer Reviewer 4	Results: Chapter 3-KQ 1 Key points	UNCLEAR. It is inappropriate to make a claim that PM women with osteoporosis will not obtain fracture risk reduction with HT. Indeed, a substantial number of the WHO cohort must have had osteoporosis (defined as morphometric vertebral fracture or T-score below -2.5.	The U.S. FDA has not approved estrogen therapy for osteoporosis therapy, only for osteoporosis prevention. Moreover, the current report did not identify reports demonstrating fracture risk reduction among menopausal women with established osteoporosis. We believe our statement is correct as written
Peer Reviewer 4	Results: Chapter 3-KQ 1 Key points	UNCLEAR This statement can easily be misinterpreted. Certainly calcium and raloxifene show much lower fracture risk reductions compared to BPs.; indeed neither calcium nor raloxifene reduce the risks of hip or non-vertebral fractures. Having no adequate head-to-head study available is not the same as "superiority has not been demonstrated".	We reworded the statement as follows: "Data are insufficient from head-to-head trials of bisphosphonates compared to calcium, teriparatide, or raloxifene to prove or disprove superiority for the prevention of fractures."
Peer Reviewer 4	Results: Chapter 3-KQ 1 Key points	UNCLEAR This statement suggests equivalence. Certainly HT shows vertebral and non-vertebral fracture risk reduction whereas neither Vitamin D or raloxifene show this. Again, the statement "there was no difference" is misleading.	We reworded the statement as follows: "Based on limited head-to-head trial data, there was no difference in fracture incidence between menopausal hormone therapy and raloxifene or vitamin D."
Peer Reviewer 7	Results: Chapter 3-KQ 1 Table 3	It helps to order the study by year instead of alphabetically	We have provided them alphabetically for ease of reference as we have done in previous reports.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 4	Results: Chapter 3-KQ 1 Alendronate	"10mg or more" is repeated many times. The "or more" should be deleted, since more than 10mg daily equivalent is not approved.	Higher doses may not be approved, but the studies reviewed did indeed administer doses that were greater than 10 mg daily, and not all of the trials reported results separately according to dose. Therefore we must leave the text as it is written. In Table 1, we make clear the available doses of all FDA-approved osteoporosis medications, including alendronate
Peer Reviewer 4	Results: Chapter 3-KQ 1 Alendronate	next to last word should be "without"	We corrected the error.
Novartis	Results: Chapter 3-KQ 1 Zoledronic Acid	On page 54 (in the Zoledronic Acid section), the following summary statement is incorrect since it refers to "probably hip fractures": "In summary, in comparison with placebo, zoledronic acid reduces the risk of clinical fractures, non-vertebral fractures, vertebral fractures and probably hip fractures." Response: The primary end points in The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial were new vertebral fractures (in stratum 1) and hip fractures (in both stratums). Treatment with zoledronic acid significantly reduced the risk of hip fracture by 41% (p=0.002)… Therefore, we request that the word "probably" be removed from the sentence on Page 54.	We have made this change.
Amgen	Results: Chapter 3-KQ 1 Denosumab	To ensure that studies supporting conclusions related to denosumab were based on the population intended for treatment, and to ensure consistency with the methodology described for the report, Amgen requests removal of the meta-analysis by Anastasilakis et al. from this report. (Anastasilakis AD, Toulis KA, Goulis DG, Polyzos SA, Delaroudis S, Giomisi A, et al. Efficacy and Safety of Denosumab in Postmenopausal Women with Osteopenia or Osteoporosis: A Systematic Review and a Meta-analysis. Horm Metab Res. 2009 Jun 17. Record ID 7517)	We made the decision to retain the meta-analysis; however, where we cite the efficacy findings, we qualify the strength of evidence for this meta-analysis and in this section as well as where we cite the adverse event findings, we clarified that one of the included studies enrolled only participants with cancer.
Amgen	Results: Chapter 3-KQ 1 Denosumab	Within the same section on page 57, the Draft Report states that Jadad scores of 2 and 0 have been assigned to publications by Bone (118) and Cummings (119), respectively… Amgen requests that the Bone study be assigned a Jadad score of 3… Amgen requests that the Cummings publication be assigned a Jadad score of 2 (1 point for randomized trial; 1 point for description as a placebo controlled trial and statements referring to unblinding of data, indicating it was a blinded trial).	We have rescored the two reports of the studies. Without further documentation, the best we can do is rescore Cummings as a 1 and leave the Bone study as a 2.

Commentor and Affiliation	Section	Comment	Response
Amgen	Results: Chapter 3-KQ 1 Denosumab and Table 16	In [Key] Question 1, the fracture reduction efficacy of denosumab is reported in the text on page 57 and in Table 16 on page 59. The values for fracture reduction provided in the Draft Report are very similar to those reported in the Cummings publication of the FREEDOM study 6. Notably, the specific numbers are referred to as Relative Risk (RR) ratio in the text and Odds Ratio in the table, even though they are the same values. In the publication of these data, Amgen reported either a RR ratio or a Hazard Ratio, depending on the type of statistical analysis performed on the data. Amgen suggests that the type of calculation provided for these fracture reduction values be consistent between the text and the table.	All published HRs and RRs were converted to ORs for purposes of comparison. The ORs differ a tiny bit from the published RRs.
Amgen	Results: Chapter 3-KQ 1 Denosumab	In the Biologics section under Key Question 1 on page 57, the summary statement as currently written for denosumab is inconsistent with those written for other agents. There is currently no conclusion for denosumab, so Amgen suggests adding the following conclusion: In summary, there is high strength of evidence that denosumab reduces the risk of vertebral fractures, non-vertebral fractures, and hip fractures in postmenopausal women with osteoporosis. This statement is consistent with the conclusions in the Summary of Evidence tables in the Executive Summary (Table A) on page ES-20 and in the Conclusions (Table 56) on page 155.	We have added a summary sentence with that information
Peer Reviewer 7	Results: Chapter 3-KQ 1 Parathyroid Hormone	In some places, the results or conclusions were not appropriately presented. For example, page 63, "For non-vertebral fractures, risk with teriparatide was not statistically different from that of placebo in two trials. this finding contrasts with the pooled analysis, which included these two trials along with three other trials, and found a statistically significant 38 percent relative risk reduction with teriparatide treatment. Results on nonverterbral fractures are therefore somewhat inconsistent." However, it is not fair to compare results from individual studies to those from a meta-analysis. If the results from the two trials were combined, the combined estimate may turn out to be significant. The investigators could not claim inconsistency without doing such analyses.	We have deleted the sentence regarding inconsistency of results and also reworded the previous sentence to reflect a reassessment of the meta-analysis.

Commentor and Affiliation	Section	Comment	Response
APTA	Results: Chapter 3-KQ 1-Physical therapy	APTA appreciates the inclusion of physical activity as an intervention that was considered for this report. Physical activity and exercise plays an important role in the multifactorial approach that should be utilized for prevention of injury in individuals with low bone density. APTA feels that the evidence used in this report is largely outdated, potentially due to the fact that it is a review of the original 2007 report. In particular, Table 31 includes studies from a very limited timeframe spanning 1989 – 2003. More recent literature on the effect of exercise and physical activity on overall fractures in other areas should be evaluated. APTA offers its assistance and support to AHRQ in helping provide resources that reflect more current evidence as it related to physical activity and exercise.	In reviewing the vast literature for this report, we identified only one controlled trial that assessed the effect of physical activity on risk for osteoporotic fracture. It was only just identified in the updated search completed after submission of the draft report, and it was not powered to detect a significant difference in fracture risk between groups. However, we have included a narrative summary of the study.
Peer Reviewer 6	Results: Chapter 3-KQ 1 and KQ 4	For teriparatide, which is the only form of PTH available in the US, you say that it probably reduces the risk of non-vert fractures, and that the results of the RCTs are inconsistent. Let me comment: the Neer trial (ref 130) and the Orwoll trial (138) were - I believe - the only two studies cited in this section that involved 1-34 rhPTH - i.e., teriparatide. The Neer trial was the pivotal clinical trial in postmenopausal women with osteoporosis, and it showed a clear reduction in non-verts. The Orwoll trial was a very short study in men that was not powered to see a reduction in non-verts. It ended early - at 12 months - because of the osteosarcoma rat data that stopped both the male and female trials. In the male study the BMD changes were nearly identical to the changes in women, and the drug was approved in men with the indication for improving BMD (not fracture reduction).	We have added text to clarify non-vertebral risk reduction in association with teriparatide: "and moderate evidence that teriparatide reduces the risk of non-vertebral fractures." on page ES-14 and 63. We would not include the study addressing men, as its outcome was BMD.

Commentor and Affiliation	Section	Comment	Response
		The PMO study in women did show the effect of both vert and non-vert reduction and that is the indication. Susan Greenspan's study (129) was with PTH 1-84, a different preparation that may have been dosed incorrectly, as that clinical trial showed vert risk reduction but not non-vert in PMO. Etah Kurland's study (137) was in men, was very small and used PTH 1-84. I have not read the Cosman study - which looks like a review - but the bulk of her work was with PTH 1-84 at the time she published that paper. Since only teriparatide (1-34) is available in the US and since the two PTH compounds are different entities given at different doses, it is not fair, I think, to say that data on non-verts in PMO patients is not consistent, at least in women. In PMO, the data we have with teriparatide shows risk reduction for both verts and non-verts. 1-84 PTH reduces vert fractures in women - but it is not approved for use in the US. The studies in men with both teriparatide and 1-84 provide little data on fractures.	We have omitted discussion of studies of PTH 1-84
Peer Reviewer 4	Results: Chapter 3-KQ 1 Alendronate vs. alendronate + calcium	This study should not be quoted since the outcome was BMD and the women did not have osteoporosis. The collection of AEs as “any clinical fracture”, although different between groups, is an inadequate measure of osteoporotic fracture risk reduction—this study outcome does not adhere to the required standard “vertebral”, “non-vertebral”, “hip” designations.	We did not consider only trials of individuals with osteoporosis. Also, we do state that we applied the criteria of Gartlehner throughout this section, and have done so in this instance too. Finally, we do state explicitly that the study assessed fractures as adverse events. The text is correct as written.
Peer Reviewer 4	Results: Chapter 3-KQ 2 Overview, BMD	What is the meaning? How does this relate to drug efficacy?	We have revised the text to indicate that this section reviews studies that assess the role of baseline BMD in predicting response to therapy
APTA	Results: Chapter 3-KQ 2-Risks for Fracture	Among the risks for fracture, one of the strongest is prior fracture, independent of BMD	We have strengthened this point in the introduction and cite studies that assess the association between prior fracture history and drug efficacy in a subsequent section of the response to this key question.

Commentor and Affiliation	Section	Comment	Response
Warner Chilcott	Results: Chapter 3-KQ 2-Key Points	In the Key Points for Key Question 2, the draft report states that risedronate significantly reduced the risk of fragility fracture in osteopenic postmenopausal women without prevalent vertebral fractures, based on post hoc analysis of a large RCT (p. 108). We think this statement, including the post hoc nature of the single-study analysis, should be added to the report's conclusions and summary tables, because the majority of fragility fractures occur in women whose bone mass is low (densitometrically osteopenic) but who do not meet the WHO BMD threshold for osteoporosis. More data are needed on fracture prevention in this large patient population.	We have added this information to Summary Tables A and 56
Peer Reviewer 4	Results: Chapter 3-KQ 2	Insert "vertebral" after "morphometric"	We inserted the word "vertebral."
Peer Reviewer 5	Results: Chapter 3-KQ 3	**Importance of gap between evidence-based agents and rate of adherence and persistence ...**the draft report states that there is a high level of evidence that numerous agents, including several bisphosphonates, reduce the risk of vertebral fractures, non-vertebral fractures and hip fractures among postmenopausal women with osteoporosis. Yet it concludes that "[e]vidence from the meta-analysis and ten of eleven observational studies suggest that decreased adherence to bisphosphonates is associated with an increased risk of fracture...the report emphasizes that the rates of adherence and persistence in the reviewed studies closely mirror the rates seen and analyzed in prior meta-analyses as well as the previous report, so this disconnect is not a new phenomenon but one that is ongoing. Therefore, this chasm between evidencebased treatments for osteoporosis and patient behavior is a considerable cause for concern."	There is an important gap between what we know "works" and the use of what works by the patients who need it. Thus we highlight the need for more research into ways of improving adherence
Peer Reviewer 5	Results: Chapter 3-KQ 3	**Is there a need for formal quality criteria?** After reading the draft report, from a patient perspective, there appears to be a need to measure adherence and persistence outside of fracture trials with more formal criteria or scales to grade the quality of adherence measurement, since poor adherence and persistence was associated with lower effectiveness of treatment agents. This may exist but this is not in my area of expertise.	We agree that adherence should be measured in the clinical setting rather than in trials, and for that reason, we summarized the findings of community-based observational studies of adherence. In general, authorities believe adherence in clinical trials is probably better than in actual practice. We have also now addressed the issue of the lack of quality criteria for observational adherence studies and the need to develop such criteria.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 5	Results: Chapter 3-KQ 3	**Potential demonstration project.** I believe that this more recent research [an evaluation of a multicomponent intervention by Solomon et al., presented at a meeting in 2010] reinforces the conclusion of the Gleeson et al. article cited in the draft report. Of considerable interest is Mitchell's discussion of the Glasgow Fracture Liaison Service structure. Although the health systems of the UK and US are vastly different, another country's successful model may provide numerous ideas for a potentially improving US healthcare. With funding for innovative models for prevention and improved health care mandated in the new US healthcare law, for those with chronic diseases, especially those like osteoporosis that are largely treatable, it appears that there is a significant opportunity to create a demonstration program around a new US model for care. If there is interest in exploring this concept, the National Osteoporosis Foundation and I would be pleased to work with AHRQ.	We appreciate this input regarding an innovative model for fracture prevention. Although interventions aimed at improving adherence were actually beyond the scope of the report, we have addressed this topic in the discussion.
Peer Reviewer 4	Results: Chapter 3-KQ 3 Key Points Bullet 4	Add a bullet stating the following: while certain variables are statistically associated with poor persistence (or adherence), none, alone or in concert, explain more than a few percentages of the variance. Thus, we cannot reasonably predict from these factors who will persist and who will not.	We agree that none of these variables explains a large proportion of the variation and that the interaction among multiple factors is not well studied. We have clarified this point in the text and bulleted conclusions by adding the following: "The frequency with which these potential barriers appear in the literature does not necessarily correspond to their importance as barriers/factors related to adherence."
Peer Reviewer 7	Results: Chapter 3-KQ 3 Key points bullet 4 and 5 and the ES	There are two points about adherence and persistence: • Many barriers have been identified to adherence and persistence. Five of the most commonly discussed include age, prior history of fracture, dosing frequency, concomitant use of other medications, and adverse effects of the osteoporosis medications • Age, history of fracture, and number of concurrent medications do not appear to have an important independent association with adherence/persistence Seems to be contradicting with each other. The first point says age, prior history of fracture and concomitant use of other medications are barriers and the second point says there is no association.	Age and prior history of fracture are among the factors most commonly studied as possible barriers to adherence. However upon investigation, it turns out they are not significant barriers. We have revised the text to clarify this point.

Commentor and Affiliation	Section	Comment	Response
Warner Chilcott	Results: Chapter 3-KQ 3b	We also recommend that section 3b (factors affecting adherence and persistence) include a discussion of oral bisphosphonate dosing. Up to 50% of patients treated with oral bisphosphonates find it a hassle to wait 30 minutes (risedronate IR, alendronate) or even 60 minutes (ibandronate) to eat or drink. Many patients are non-compliant with this requirement and do not wait… [which] will impair product efficacy.	Although we list difficulty taking medication as a barrier that has been studied, in the table of barriers, it is not one of the more common ones found in the literature.
Amgen	Results: Chapter 3-KQ 3b	Key Question 3B on page 122 examines factors affecting adherence and persistence and lists patient preference as an important factor. In the introduction to the evidence review for Key Question 3B, it is stated in the second paragraph that "…patient preference studies reported patients preferred less frequent dosing of medications." Amgen conducted two randomized, double-blind, controlled trials comparing denosumab and alendronate that included the Preference and Satisfaction Questionnaire (PSQ).(Kendler Osteoporosis Int. 2010) This validated instrument assessed patients' preference, satisfaction, and degree of bother with each regimen after 12 months of therapy.(Gold 2008) Over 93% of patients completed at least one item in the PSQ and were included in the evaluation. Patients preferred and were more satisfied with the 6-month subcutaneous injection than with the weekly oral tablet. In patients reporting a preference, significantly more patients in both study arms preferred the 6-month subcutaneous injection to the weekly oral tablet (63% to 65% vs 19%; P<0.0001). A similar result was reported in a third randomized, open-label, crossover study Kendler Osteoporosis Int. 2010). Based on this evidence, Amgen requests that this report include an additional statement on the preference for a 6-month subcutaneous injection compared with a weekly oral tablet.	We did not systematically address patient preference and included only those studies that measured adherence, persistence, and/or compliance.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Results: Chapter 3-KQ 1- KQ 3b	Another example, page 123, History of Fracture, the conclusion is that "Therefore, the literature we identified, including the one US study, does not point to an association between prior history of fracture and medication adherence or persistence." However, two bigger studies identified an association. For the smaller studies, though no-significant, the direction association was not stated. If these studies were appropriate to be combined and the directions of association were consistent, then it is possible to get an association from a meta-analysis. The investigators did not perform necessary analysis to reach their conclusion.	We did not do any meta-analyses, mostly because the studies (and how they measure adherence, how they report it, the control variables they include, etc) are incredibly heterogeneous; we did not judge them sufficiently clinically similar to justify meta-analysis. We added a number of studies that addressed the role of history of fracture and discuss the finding that associations are mixed.
		In general, the report failed to recognize that for some outcomes, esp. rare ones, while each individual study may not show a significant association, it is possible to get a significant association through appropriate meta-analyses. For the individual studies, it could be a power issue, instead of lack of association. Of course, it could be lack of association, too. It is just that such conclusion should be reached through adequate and proper analysis of available data.	The key word is "appropriate." We performed all the meta-analyses that we judged were appropriate based on the analyses conducted in the original report and the fact that this report represents an update of that report, and did not perform any we judged inappropriate.
Peer Reviewer 7	Results: Chapter 3-KQ 3b-History of Fractures	"found that osteoporotic fracture or hospitalization for osteoporosis in the year before the start of therapy was associated with increased odds of compliance (adjusted OR 0.65; 95% CI 0.47-0.88), as measured by MPR." -Increased odds with OR = 0.65?	We revised the wording to "decreased the odds of non-compliance."
Chapell, Richard	Results: Chapter 3-KQ3	The EPC is inconsistent in its reporting of the potential for bias in industry-sponsored research. One study is described as "written by the makers of riesedronate", while another is simply described as "industry-funded." Another was "funded and authored in part by Merck.". Only a single company, Merck, is singled out by name as a potential source of bias. We believe this to be potentially prejudicial, and request that consistent language be used when assessing the potential for bias in industry-sponsored trials	We have removed references to specific manufacturers, both by name and product, and have made all description consistent ("industry funded").
Peer Reviewer 4	Results: Chapter 3-KQ 3b	This study identified BP users through a pharmacy database, but used self-report (telephone interview) for their measures. The study had only a 33% response rate and the authors consider it not generalizeable. The outcome measure was NOT discontinuation for 7 months.	We have retained the narrative description of the study but increased the emphasis on the poor response rate.

Commentor and Affiliation	Section	Comment	Response
Amgen	Results: Chapter 3-KQ 3c	In Key Question 3C on page 126, Amgen suggests making a minor correction from "<" to ">" in the statement, "A third study found that women who were adherent (MPR>80%) had a 16% lower fracture rate."	We corrected the error.
Peer Reviewer 7	Results: Chapter 3-KQ 3c	"However, in five studies that showed a decrease risk of fracture with increasing compliance, the relationship between compliance and fracture risk was non-linear" is confusing for the readers. -Should explain what non-linear is.	We revised the sentence to read, "…no dose-response relationship was observed between compliance and fracture risk."
Chapell, Richard	Results: Chapter 3	Font error "?80%"	We inserted the correct symbol (≥).
Peer Reviewer 4	Results: Chapter 3-KQ 3c	Why compare adherent subjects to everyone in study—why not to those with lesser degrees of adherence?	According to the article "limiting the analyses to the cohort to the 7050 women who were at least 70% adherent to the study treatment on the basis of pill count did not alter the results." We revised the text accordingly
Peer Reviewer 4	Results: Chapter 3-KQ 3c	HR 10.32 typo? CIs suggest this is not a typo—what interpretation can one give to this?	The HR is not a typo but it is not the HR associated with the effect of adherence on those with prior fractures compared with those with no prior fractures. Rather it is the HR associated with the effect of prior fracture on subsequent fracture; the text was revised.
Amgen	Results: Chapter 3-KQ 4	Amgen recognizes that Key Question 4 addresses the short- and long-term adverse events of therapies used to treat or prevent low bone density and osteoporotic fracture, and that a technical expert panel and other subject matter experts identified adverse events of interest for this report… we would like to remind AHRQ that the FDA-approved product information, Amgen previously submitted to AHRQ, provides additional detail about risk information.	We have added the findings from the MA by Anastasilakis as well as the newer MA by Toulis and Anastasilakis and the reference to the FDA REMS
Peer Reviewer 4	Results: Chapter 3-KQ 4 Key points Bullet 5	delete section on "mild CV events" (see above)	We have re-analyzed the data reported for hot flashes and flushing, as some studies categorized these events as mild CV events.
Peer Reviewer 4	Results: Chapter 3-KQ 4	Mention the observational literature linking alendronate with increased risk of PUBs.	For this review, we relied solely on trial data for all but very rare adverse events. As opposed to the observational literature, we did not find a statistically significant increase in serious GI side effects for alendronate.
Peer Reviewer 4	Results: Chapter 3-KQ 4	Mention serious skin infection, cellulitis requiring hospitalization, with denosumab. This is included in the PI by the FDA.	We have added the findings from the MA by Anastasilakis as well as the newer MA by Toulis and Anastasilakis and the reference to the FDA REMS

Commentor and Affiliation	Section	Comment	Response
Chapell, Richard	Results: Chapter 3-KQ4	An assessment of atrial fibrillation among patients taking alendronate was recently published. Please include it in the systematic review: E. Barrett-Connor et al., Alendronate and atrial fibrillation: a meta-analysis of randomized placebo-controlled clinical trials. Osteoporosis International, ePub. ahead of print, March 3, 2011.	We have added this MA to the section of the report that presents data on AF and bisphosphonates

Commentor and Affiliation	Section	Comment	Response
Chapell, Richard	Results: Chapter 3-KQ 4: Atrial Fibrillation	The conclusion is made, page 132, line 23, that there is a significant increase in atrial fibrillation with the use of zoledronic acid. This is largely based on the original study published by Black et al, in which there were 50 patients who developed Atrial Fibrillation. The vast majority developed it 30+ days after the infusion, which makes it difficult to attribute to the drug. The other study by Lyles et al, using the same drug in a group of patients with hip fracture found no increase. In the new Meta analysis, cited by the authors, there were again no increase incidents with all bisphosphonates. The FDA, in their review of all of the data in 2007 and 2008 (on their web page), concluded that it was unclear how this should be interpreted and did not believe that healthcare providers or patients should change their prescription practices. Again, the observation is there, in that one particular trial, but occurred at a later date after the treatment, and the relation to the therapy is hardly proven.	The text has been revised extensively and now reads as follows: The original report identified two large trials that showed a trend toward an increased incidence of atrial fibrillation (AF) with alendronate and a significantly increased incidence with once-yearly zoledronic acid relative to placebo, respectively.[111,351] The current report identified several new original studies and systematic reviews. A meta-analysis of all RCTs of at least 3 months duration on the use of alendronate to treat or prevent osteoporosis by the Merck Corporation (32 trials, more than 17,000 participants) found no effect of alendronate on the incidence of atrial fibrillation.[352] A pooled analysis of the results of the pivotal trials of ibandronate showed no effect on the incidence of AF.[353] One new study of zoledronic acid was pooled with the original study to show an increase in the incidence of AF with zoledronic acid (pooled OR 1.45, 95% CI 1.14, 1.86).[113] Five systematic reviews were identified that combined studies of different bisphosphonates. Two 2009 systematic reviews that conducted meta-analyses of the same four trials and two observational studies reported a significant association between bisphosphonate exposure and the risk for serious atrial fibrillation.[354,355] A 2009 Bayesian meta-analysis that included four original reports of RCTs (including the two large trials described above), two post hoc analyses of combined data from multiple RCTs, and three observational studies found a non-significantly increased risk of AF among bisphosphonate users (pooled OR for overall risk of AF from RCTs 1.18, 95% CI 0.84, 1.66; pooled OR for serious AF from RCTs 1.59, 95% CI 0.61, 3.75; pooled OR for observational studies 1.25, 95% CI 0.98, 1.73).[356] A 2010 systematic review of seven observational studies found no evidence for an association between bisphosphonate use and increased risk for atrial fibrillation; however, the I-squared statistic suggested moderate heterogeneity.[357] A 2010 systematic review of 16 RCTs, observational studies, and prior systematic reviews meta-analyses that included some of the same studies as the systematic prior reviews identified for the original report found some evidence of an association of bisphosphonate use with increased risk for AF.[358] Consistent with this evidence, in March 2010, the FDA issued a follow-up to its 2007 safety review, noting the inconsistency in the data and requesting that providers and patients report side effects.[359]

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 3	Results: Chapter 3-KQ 4-Gastrointestinal adverse events	In the discussion of gastrointestinal adverse events (p. 133), the report might clarify the statement that “Perforations, ulcerations, and bleeds (PUB) were reported in trials of all the bisphosphonates except zoledronic acid” by inserting “for active and placebo groups” after “(PUB)”. The change would clarify that reporting a PUB event means that data were collected; it does not signify a higher reporting rate in the active-treatment group than the placebo group.	We added the wording suggested by the reviewer.
Chapell, Richard	Results: Chapter 3-KQ4-Atypical Fractures	The statement that the FDA "updated the risk of atypical fractures to the Warnings and Precautions level" is incomplete and therefore misleading. A complete discussion of the cited document (Reference 375) would also note that the FDA stated that "Although it is not clear if bisphosphonates are the cause, these unusual femur fractures have been predominantly reported in patients taking bisphosphonates." Please include this statement in the discussion of the FDA position on atypical fractures.	We have added the statement as well as descriptions of newer studies.
Warner Chilcott	Results: Chapter 3-KQ 4-Atypical Fractures	In the discussion of atypical fractures (p. 135), the report should clarify the findings of the task force of the ASBMR regarding the risk/benefit analysis by adding language from the report as follows: “Based on published and unpublished data and the widespread use of BPs, the incidence of atypical femoral fractures associated with BP therapy for osteoporosis appears to be very low, particularly compared to the number of vertebral, hip and other fractures that are prevented by BPs. Moreover, a causal association between BPs and atypical fractures has not been established.” See “Results and Conclusions” of ASBMR Report.	We have added this language.
Warner Chilcott	Results: Chapter 3-KQ 4-Osteonecrosis of the jaw	In the discussion of osteonecrosis of the jaw (p. 135-136), the report might clarify the current consensus of the referenced studies with language such as: “To date, there is no evidence from controlled clinical trials or post-approval evaluation concluding there is any cause or association between bisphosphonate treatment and ONJ.”	We have left the final sentence in this section of the Results chapter as is, because the data we report are confined to the use of bisphosphonates for osteoporosis therapy and because the Results chapter is not the section of AHRQ reports where we draw conclusions.
Warner Chilcott	Results: Chapter 3-KQ 4: SERMs and Mild Cardiovascular Events	Here the authors cite four papers. After looking at the papers (page 139, line 45), it is hard to say what the mild cardiovascular events were. In one, they were comparing alendronate to raloxifene. Another was with benzedoxifene. It would appear that in all cases that these probably represented hot flashes. I think this should be eliminated.	We have re-analyzed the data reported for hot flashes and flushing, as some studies categorized these events as mild CV events.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 3	Results: Chapter 3-KQ 4: SERMs	Results for Raloxifene and BC (page 140) is not consistent with other studies (Nelson et al. Systematic Review: Comparative Effectiveness of Medications to Reduce Risk for Primary Breast Cancer. Ann Intern Med. 2009; 151:703-715).	It was not within the scope of this report to assess the literature on medications to reduce the rates of primary breast cancer; the AEs we report are limited to those identified in studies that reported on the use of osteoporosis therapeutic agents. Thus the Nelson article would not have been identified by our searches, and not included in our review.
Peer Reviewer 7	Results: Chapter 3- KQ 4: SERMs--Sweats/Fever/ Hot Flashes	Why do the results from the two meta-analysis somewhat differ? Need to explain.	The statistician originally ran two separate meta-analyses, believing that vasomotor flushing was different from hot flashes, as some studies reported the symptom with one term and others reported it with the other term. She subsequently reran the meta-analysis with all studies that reported hot flashes/flushing/vasodilatation, and only one pooled risk difference and odds ratio are now reported.
Chapell, Richard	Results: Chapter 3-KQ4-Calcium and Vitamin D and serious cardiac events	The assessment of the effects of calcium and vitamin D treatments on risk for serious cardiac events contains numerous errors and should be revised. The review cites an increased relative risk of 1.27, citing an article, Bolland et al., 2010 J. Clin. Endocrinol. Metab. The cited article contained no such analysis, and reported no such conclusion. A similar, uncited article by the same lead author published in the British Medical Journal (BMJ 2010;341:c3691) did report this analysis. However, the analysis excluded studies in which calcium and vitamin D were coadministered.	First, we corrected the reference, Second, we have reread the meta-analysis as well as the letters and commentaries, have revised the description of the meta-analysis extensively to include a discussion of the limitations, and have revised the conclusions accordingly.
Chapell, Richard	Results: Chapter 3-KQ4-Calcium and Vitamin D and serious cardiac events	This group of studies includes the US Womens Health Initiative Study (Hsia J et al. Circulation. 2007;115:846-854). The WHI study included 36282 postmenopausal women and the coronary heart disease death hazard ration associated with calcium/vitamin D supplements was 1.04 with a 95% CI, 0.92 to 1.18. Cerebrovascular disease risk was 0.92 (95% CI 0.82 to 1.10). That is, a finding of no benefit and no risk. Please revise the reference list to cite the correct Bolland study and add studies of combined calcium and vitamin D, including the WHI study, to the review. As this will probably alter the conclusions of this portion of the review, please also revise them on pages viii, ES17, ES22 and 158.	(the comment in this row is part of the comment by Dr. Chapell in the row above; thus our response in the row above also pertains to the comment in this row)

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Results: Chapter 3-KQ 4: Calcium Effect	The evidence for the calcium effect comes from a Meta analysis outlined on page 145, line 14 following. This is the first Meta analysis to find evidence of increased myocardial infarction with calcium supplementation. There were a number of letters published in subsequent volumes of the BJM which outlined the problems with this particular Meta analysis, indicating it cannot be generalized. These include comments from Dr. Heaney and Lappe and Dr. Dawson Hughes, among others. The Meta analysis to a great extent is based on unpublished results by the authors. There is no evidence that calcium plus vitamin D has such an effect, nor dietary calcium intake.	(the comment in this row is part of the comment by Dr. Chapell in the row above; thus our response in the row above also pertains to the comment in this row)
Peer Reviewer 7	Results: Chapter 3	The myocardial infarctions were not an end point and were not verified. Results from Lappe and Heaney cited in their letter from a somewhat similar population found no increase. This observation is important because calcium supplementation is widely used, although generally with vitamin D. I feel however this is certainly not strong evidence. I believe it was judged as moderate, and perhaps should be no more than weak evidence, if at that level. If you are in agreement, changes should be made on page 30, line 20; page 17, line 10; page 22, line 29; and page 161, line 44 as well.	Please refer to our response to the comments by Dr. Chapell in the two preceding rows.
Peer Reviewer 3	Results: Chapter 3-KQ 5 Bullet 5	UNCLEAR This statement needs recasting. May I suggest: Evidence from one large RCT that tested the efficacy of alendronate for 10 years versus 5 years showed no additional benefit of continuing the additional 5 years in reducing the risks of morphometric vertebral fractures or non-vertebral fractures. There was a possible benefit for clinically apparent vertebral fractures. There was no benefit of continuing unless baseline BMD was below -2.5 or one or more vertebral fractures were present at the start of treatment.	We have revised the text according to the reviewer's suggestion.
Peer Reviewer 4	Results: Chapter 3-KQ 5a.2-Prior Meta-Analyses	Many results for monitoring BMD are confusing. See next 4 rows. "That is, based on improvement in BMD, treatments actually reduced fracture risk by 45%." -Based on what the predicted risk reduction should be 20%?	The authors used logistic regression models to estimate the proportion of the reduction in risk of an outcome (e.g., vertebral fracture) explained by the effects of treatment on an intermediary variable (spine bone mineral density). The proportion of the reduction in the risk of fracture (p) that was explained by changes in a marker was estimated as follows: $p = (1-\beta^*/\beta)$ where β = log (unadjusted odds ratio [OR]) and β^* = log (OR adjusted for bone mineral density). We have added this to the report.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 4	Results: Chapter 3-KQ 5a.2-Alendronate	"...among participants taking at least 60% of assigned study medication, women who gained 0 percent to 4 percent of BMD after 1-2 years during treatment had a decrease in vertebral risk of 51 percent (OR=0.49, 95% CI 0.30-0.78) after 3-4 years of follow-up. However, women who had a 60 percent lower risk of vertebral fractures (OR=.40, 95% CI 0.16-0.99) compare to their counterparts assigned to placebo" -These results are about comparing alendronate vs. placebo, not on monitoring BMD?	We felt the results provided information about monitoring, because they demonstrate that regardless of the change in BMD during therapy, significant fracture protection is provided by alendronate therapy, and that protection is even significant among women who lose BMD during therapy
Peer Reviewer 7	Results: Chapter 3-KQ 5a.2-Risedronate	"Changes in lumbar spine femoral neck explained 12% (95% CI 2%-21%) of the reduction in nonvertebral fracture risk associated with risedronate therapy. Changes in femoral neck BMD explained 7 percent (95%CI 2%-13%) of reduction in nonvertebral fracture risk associated with risedronate therapy." It is not clear where these numbers come from? Are you talking about attributable risk?	IT is not attributable risk. The proportion of the treatment effect of risedronate (defined as the difference between the risedronate and placebo groups) on nonvertebral fracture that was explained by changes in BMD was estimated using a method that was an extension of a method proposed by Li et al. The estimate is obtained by calculating the ratio of the regression coefficients, where the numerator is the risk reduction explained by the surrogate, and the denominator is the overall risk reduction by treatment. We have added this description to the text.
Peer Reviewer 7	Results: Chapter 3-KQ 5a.2-Raloxifene	"For any percentage change, either an increase or a decrease in femoral neck of lumbar spine BMD at one year or three years, women assigned to raloxifene had a statistically significantly lower vertebral fracture risk compared with placebo-treated women." -What does this sentence mean?	We removed the sentence as the subsequent sentence adequately conveys our meaning: "The reduction in fracture risk with raloxifene was similar regardless of percentage change in lumbar spine or femoral neck BMD at three years."
Peer Reviewer 7	Results: Chapter 3-KQ 5a.2-Raloxifene	"The magnitude of change in BMD during raloxifene therapy accounted for 4 percent of the observed vertebral fracture reduction, i.e. 96 percent of reduction in vertebral fracture risk in women assigned to raloxifene therapy was unexplained." Are you saying that it is not clear how raloxifene works to reduce fracture? Such statement would be very confusing to the readers. Anyway, these results need to be clarified.	It is well known that raloxifene works as an anti-resorptive. In our summary page (which now appears on page 151), we state that" The reason for the low association of changes in BMD and fracture risk reduction during pharmacotherapy appears to be that the majority of fracture risk reduction results from improvements in non-BMD determinants of bone strength."
Peer Reviewer 7	Results: Chapter 3-KQ 5a.2-Risedronate	The percentages in parentheses are confusing. I assume these refer to the proportion of women who suffered a non-vertebral fracture over 3 years. Best to say that and avoid use of the word "incidence" or instead use "cumulative incidence".	We added the following text for clarification: "... (hazard ratio 0.93, 95% CI 0.68-1.28). This study reported that fracture risk was similar (about 10 percent), in risedronate-treated women whose increases in BMD were <5 percent, (the median change from baseline) and those whose increases were ≥5 percent.475 Thus, greater increases in BMD did not necessarily predict greater decreases in vertebral fracture risk."

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	Results: Chapter 3-KQ 5b	Long-term (7-year) follow-up data are available for risedronate. Thus please consider including the following data: In a comprehensive time-to-event analysis of data over 5 years of therapy (the original VERT-MN study and the 1st extension), risedronate (n=135) resulted in a 50% reduction in the risk of vertebral fractures (p=0.001) and a 37% reduction in the risk of non-vertebral fractures (p=0.022), both compared to placebo (n=130) (Sorensen 2003)	On page 150 lines 40-41 we indicated that for this key question, we were looking at longer (3-5 years of therapy) vs. shorter durations of therapy. The article cited reports on fracture protection in years 4 and 5 based on the total treatment period, but there is no statistical comparison of 5 yrs vs. 3 yrs of therapy.
Peer Reviewer 4	Results: Chapter 3-KQ 5b	The risks of vertebral and non-vertebral fractures in patients taking risedronate versus placebo over 5 years were similar to those at year 3 (Reginster 2000, page 86, Table 2; Sorensen 2003, page 125)	Likewise, as with the Sorensen study, there was no statistical comparison of 5 years to 3 years.
Warner Chilcott	Results: Chapter 3-KQ 5b	Participants in years 6 and 7 (i.e., the 2nd, open-label extension of the VERT-MN study) included 83 patients who had been on risedronate for the entire 7 years and 81 patients who had been on placebo for 5 years and switched to risedronate for the 2nd extension. In years 6 and 7, the vertebral fracture incidence was similar between the 7-year risedronate group and the placebo/risedronate group (i.e., those that received risedronate only during years 6 and 7) (3.8% for both groups) (Mellstrom 2004).	Again, there was no statistical comparison between longer and shorter time periods.
Warner Chilcott	Results: Chapter 3-KQ 5b-Risedronate	simplify ; “as opposed to primary prevention”.	We have made this change.
Warner Chilcott	Summary and Discussion: Chapter 4-Overall	Yes the findings were clearly stated, and their conclusions are clear regarding areas of future research.	No response needed.
Peer Reviewer 4	Chapter 4:Overall	These seem quite reasonable with the exceptions of those noted above.	No response needed.
Peer Reviewer 2	Summary and Discussion: Chapter 4-Discussion/Conclusion	Testing for publication bias is not mentioned in the methods section. Do the investigators perform Begg's and Egger's tests using all studies for Benefits? The value of such tests has been limited when the number of studies is small. One limitation of this review is the lack of adequate data synthesis. The discussion part is still basically repetition of results and not many implications are stated. Future research section looks good to me.	We could not test for publication bias in the analysis of benefits as we did not do new meta-analyses for efficacy.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 3	Summary and Discussion: Chapter 4-Discussion	In your summary it is stated that "Studies directly comparing the antifracture effects among various bisphosphonates do not support the effectiveness of one bisphosphonate over another." I'm disappointed to see once again that all BPs are lumped together. Obviously, BPs share several common properties as a drug class. However, as with other families of drugs, there are obvious chemical, biochemical, and pharmacological differences among the individual BPs… Likewise there are differences in their duration of action, and effects on fracture reduction. We reviewed this recently. See Russell RG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporosis Int 2008;19:733-59.	The citation in question could not be included in our analysis as it was not an RCT reporting fracture outcomes. Our analyses were limited by the available literature, which (in general) do not support that there exist conclusive differences in effectiveness. For reasons we described, comparing findings among BPs across studies in the absence of intrastudy comparisons is not desirable. We have now addressed this point in the Discussion section.
Peer Reviewer 7	Summary and Discussion: Chapter 4-Discussion	It is very misleading for practitioners for you to imply that ibandronate has an effect in reducing nonvertebral fractures when the controlled RCTs clearly showed it didn't. If you accept the type of dubious evidence on which the alleged evidence for a non-vertebral benefit of ibandronate is based you should also consider the arguably stronger data that shows that risedronate works faster than the others in reducing fractures, without reducing bone turnover as much as alendronate does.	We agree, and have revised the text accordingly on the discussion page. By omitting ibandronate from the statement regarding non-vertebral fractures.
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	It is also potentially harmful for patients to suggest that prescribing any of the BPs reduce hip fractures when only 3 of the four have been clearly shown to do this. If someone on ibandronate gets a hip fracture how could a prescribing doctor defend their position in court litigation brought by the patient?	We cannot find any place on page 160 where we say that prescribing any of the bisphosphonates reduce hip fractures. The text on page 160 reads "There is a high level of evidence that alendronate, risedronate, denosumab, and zoledronic acid each decrease the risk of hip fractures among postmenopausal women with osteoporosis."
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	The pharmacological differences have other clinical consequences. For example, since the effects of risedronate wear off within a year of stopping treatment whereas the effects of zoledronate and alendronate may persist for several years, it would be very unwise to think that drug 'holidays' can be considered as having similar effects for all the BPs.	We added a statement to this effect in the Future Research Section, which is the section in which we discuss drug holidays: "Could the efficacy of drug holidays vary according to pharmacologic profiles (e.g. route or frequency of administration) of the various bisphosphonates? And should all therapies be subject to a holiday, a point raised by a recent basic science analysis of denosumab?"

Commentor and Affiliation	Section	Comment	Response
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	Another problem is that there is much fear over using BPs, based on occurrence of ONJ, atrial fibrillation (AF), and more recently the atypical femoral fractures. This deters patients from accepting and complying with treatment. ONJ in reality is coming to be seen as a cancer related problem, and probably a non-issue for BPs used in osteoporosis, although the fear among patients persists. The AF and esophageal cancer scares also probably have no basis based on all current evidence. And the story about atypical fractures suggests that alendronate may be more a potential culprit than the other BPs, but even so the evidence for a convincing causal relationship doesn't exist.	We have added a statement to the Conclusions section in both the executive summary and chapter 4 that conclusive evidence of a causal relationship is lacking. Based on the evidence we reviewed, we believe there is inadequate evidence to single out alendronate as more of a culprit than other bisphosphonates.
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	Denosumab is rightly mentioned as an important new and efficacious treatment for osteoporosis. But again the opportunity for a proper scientific evaluation of how this treatment differs from existing treatments is completely missing. The simple observations are that denosumab reduces bone turnover much more than bisphosphonates, but if treatment is stopped there is a rapid and extensive resumption of bone resorption resulting in the potential loss of treatment benefit. These issues were discussed in a recent review. Baron R, Ferrari S, Russell RG. Denosumab and bisphosphonates: Different mechanisms of action and effects. Bone. 2011 Apr 1;48(4):677-92. Epub 2010 Dec 9.	We cannot include data from studies that do not meet the inclusion criteria, among which are that the study must report fractures as a primary outcome; we now address this point in the section on Future Research.
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	In considering the overall risks and benefits of treating osteoporosis it's important to mention the reduced mortality seen in at least 5 different studies, as well as the reported reduced rates of breast cancer and colon cancer (see Rennert and Chlebowski references in full set of comments).	These studies did not meet inclusion criteria, as we included only original RCTs in the analysis of efficacy.
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	APTA emphasizes that any identified shortage in randomized controlled trials (RCTs) or perceived lack in quality evidence comparing the effectiveness of physical activity/exercise represents an opportunity upon which AHRQ should pursue further investigations. The value of these interventions should not automatically be assumed inconsequential, but rather simply understudied. The statement "No RCTs of exercise interventions have demonstrated a reduction in fracture risk" used in the Discussion section of AHRQ's report is deeply concerning, and seems inconsistent with more current evidence that is being produced.	We have identified one new RCT of physical activity that met the inclusion criteria for the report and have included that study. We point out in the Conclusions and Discussion sections that the data are insufficient to identify an effect and that no trials have compared the effects of physical activity to those of pharmacological agents.

Commentor and Affiliation	Section	Comment	Response
Russell, Graham	Summary and Discussion: Chapter 4-Discussion	The Discussion section on page 161 states that the role of once-yearly bisphosphonates in improving adherence is unclear and that potential improvements must be balanced by potential barriers. Amgen agrees with the statement that "the role of once-yearly bisphosphonates in improving adherence is unclear." Notably, this is the first instance in the report that this statement is made and Amgen suggests including additional detail related to this statement here and within Key Question 3 on page 114. For example, including a statement that the only available once-yearly bisphosphonate is administered as an intravenous infusion would help readers understand the administration differences among these drugs. Furthermore, the continuation of the statement "balanced by potential barriers" should be better described within Key Question 3 on page 114. Currently, the statement could be interpreted to suggest that there are multiple barriers that could offset the adherence improvement, yet only one barrier is listed. Additional context for this statement would be useful for the reader.	Unfortunately we identified only once study that assessed adherence with once-yearly zoledronic acid, but data were available only for 1 year. Thus, we can't say at this time whether a once-a-year drug improves adherence. We have clarified the point about barriers.
APTA	Summary and Discussion: Chapter 4-Discussion	Serious skin infections (cellulitis) is listed in PI as FDA warning and should be mentioned.	We have added the appropriate data and FDA REMS to the report text.
Amgen	Summary and Discussion: Chapter 4-Future Research	Revise the conclusion regarding comparative effects of therapies. Clinical guidelines and product labeling differentiate products within the bisphosphonate class based on whether each product prevents vertebral, non-vertebral, and/or hip fractures, as well as efficacy in specific patient populations. This matters to patients and their providers. For example, hip fractures are costly, deadly (20%), and are often associated with a loss of independence and impairment of quality of life. Vertebral fractures can be painful and debilitating but comprise only 27% of osteoporosis-related fractures in the US and 6% of costs (Burge 2007). Evidence does not support the conclusion that "…the issue now seems settled that treatment with any of the FDA-approved agents discussed in this report will decrease the risk for all or most kinds of osteoporotic fractures for postmenopausal women with established osteoporosis" (p. ES-24, p.162), nor the implication that the difference between preventing "all" or "most" kinds of fractures is inconsequential.	The sentence has been deleted.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 4	Summary and Discussion: Chapter 4-Future Research	The draft update concludes that "any comparative differences, if they exist at all, will be small, at least between the bisphosphonates." This statement is inconsistent with clinical guidelines developed by physicians, based on years of research and clinical experience with their patients (AACE, ACP, ACR)… the AHRQ statement may prompt health plans to limit access to osteoporosis therapies. We propose that AHRQ consider revising this statement to more accurately reflect differences among products in proven fracture efficacy – both vertebral and non-vertebral – enabling providers to select an appropriate therapy for each patient's individual needs.	This sentence has been deleted.
Warner Chilcott	Summary and Discussion: Chapter 4-Future Research	replace "did not occur" with "was not widely reported"	We revised the text as suggested.
Warner Chilcott	Summary and Discussion: Chapter 4-Future Research-Who should we treat	The AHRQ Draft Report discusses several areas for potential research, one of which recommends that further research should be conducted on who should be treated for osteoporosis. NOF agrees… [they include their criteria for who should be considered for treatment – add to discussion?] NOF applauds the AHRQ Draft Report's call for further research regarding osteoporosis and would be glad to further discuss this issue.	No response needed
Chapell, Richard	Figure 1	Under interventions, 'Biologicals-Denosumab' should be added as well	Denosumab has been added to Figure S-1 and Figure 1.
Chapell, Richard	Table 1	Table 1 does not include the injectable form of ibandronate	Injectable ibandronate was added to the table.
Peer Reviewer 4	Appendix C: Evidence table C-6: Adverse Events	This table is mislabeled. It contains data on calcium and Vitamin D AEs, not Estrogen.	We are not sure we understand the question, since the evidence table does include studies on estrogen.
NOF	Appendix C: Evidence table C-6: Adverse Events	These list AEs of lasofoxifene and bazedoxifene. Yet these drugs are not included in the efficacy section. Delete.	These drugs have been omitted from the evidence table as they were deleted from the report.
Peer Reviewer 4	Appendix C: Evidence table C-6: Adverse Events	Preos, PTH 1-84 is not FDA approved. Delete.	PTH 1-84 has been omitted from the evidence table as it has been deleted from the report.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 1	General	General Comments: Very useful and well written document - As a reviewer of other evidence reports, this is one of the best that I have reviewed	No response needed.
Peer Reviewer 2	General	General Comments: The report offers important insights into the state of the literature and current knowledge gaps. it is a thorough summation of the literature to date	No response needed.
Peer Reviewer 3	General	General Comments: This is a generally well done update of their previous Meta analysis. I think it does have usefulness for the clinicians who are treating osteoporosis. The questions have been clearly stated. I think there are only three areas of concerns in the adverse events reported, which I discuss below. It is important that these be corrected, particularly in the executive summary, which probably more people will read than the full report.	No response needed. (see below)
Peer Reviewer 4	General	I shall restrict my comments to the material found on pages 28 and those subsequent. Of course, these criticisms and suggestions apply to the same text that is repeated elsewhere (e.g. executive summary).	No response needed.
Peer Reviewer 5	General	The report is clearly written and well-documented. The Executive Summary and the Introduction (Chapter 1) allow a reader to briefly review the contents and conclusions of the report as well as understand the events and environment leading to this most recent update. As a reviewer representing patients, my comments are focused on Question 3 and represent my views alone	No response needed.
Peer Reviewer 4	General	Many of the statements, while adhering to the logic of the analyses, can be easily misinterpreted. The shorthand and argot used for the analyses creates a problem with clarity. Probably due to the overwhelming numbers of publications, the need to make definitive statements, the writers have made unclear statements. This is especially troublesome when these statements are directly copied into the Executive Summary. This is quite important because most Readers will not go beyond the Summary.	Since this comment did not highlight the specific concerns, we were unable to formulate a response.
Peer Reviewer 4	General	“Mild cardiac events”, as defined for these analyses, includes hot flashes or menopausal vasomotor symptoms. Designating a hot flash as a cardiac event of any severity is misleading. Especially in the case of raloxifene, a drug that increases hot flashes (perhaps 20-25% reporting this), doing this creates the impression that this drug could have real harm for the heart. I would suggest deleting this designation altogether.	We have eliminated this category had substituted "vasomotor flushing."

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 6	General	Overall, I think you have done a masterful job, and I hope the final document will be a success. I did have two fairly large concerns, though. One has to do with teriparatide, the other with raloxifene (see below)	Please see responses to specific comments below.
Warner Chilcott	General	Report failed to include risedronate sodium (Atelvia), approved in 2010, a once-weekly delayed release formulation	The scope of our review was limited to fracture outcomes. We looked for but did not find trials that evaluated the efficacy of Atelvia with respect to fracture outcomes.
Warner Chilcott	General	We agree with AHRQ's decision to remove etidronate from the report.	No response needed.
Russell, Graham	General	Firstly I commend you on the work done, and the difficulty of the task	No response needed.
Russell, Graham	General	I'm concerned about the lack of scientific evaluation of the pharmacology of the various drugs. For example all the bisphosphonates are not the same, even if their overall clinical effects are hard to differentiate. By grouping them together you miss important potential consequences of differences among them.	A review of studies examining the characteristics of the drugs was beyond the scope of this project. However, we added a brief description of the sequence of development of the bisphosphonates.

Commentor and Affiliation	Section	Comment	Response
ISCD and AACE	General	The methodology employed by the panel introduces important biases into the evidence review, relying on assumptions that are not justified in the general population. The limitations of the review outlined below constitute reasons to reject the conclusion that use of BMD to monitor treatment response in osteoporosis is unsupported by evidence. [the following is a summary of their 3 comments] 1. Trial subjects and patients in practice differ in important ways. 2. Poor adherence is a major challenge to successful treatment of osteoporosis. 3. We question AHRQ's conclusion that patients experiencing BMD declines on antiresorptives enjoy equivalent fracture protection to those whose BMD remains stable or increases (see discussion of Watts, 2004; Chapurlat, 2005).	We agree that trial subjects and patients in practice may differ in important ways. However, we are not aware of any evidence proving that BMD monitoring predicts fracture efficacy more strongly in clinical practice than in RCT participants. We are also not aware of any RCTs showing that serial BMD monitoring increases adherence. We did not conclude that patients experiencing BMD declines in antiresorptives enjoy equivalent fracture protection to those whose BMD remains stable or increases. We could not find such a conclusion stated in our report. We do, however, say that the change in BMD during serial monitoring only accounts for a small proportion of the anti-fracture benefit of osteoporosis pharmacotherapy. This has been shown in several analyses of RCT data that we summarize in the report on pages 148-149. Moreover, these studies showed similar reduction in vertebral fracture risk regardless of change in BMD (ref 405 Sarkar JBMR 2002), 3) similar decreases in vertebral fracture risk across categories of femoral neck BMD change (ref 406 Watts JBMR 2009), and no difference in the incidence of nonvertebral fracture between women whose BMD decreased and those whose BMD increased i.e. changes in spine or femoral neck BMD did not predict the degree of reduction in nonvertebral fractures (Ref 403 Watts JBMR 2005). The Watts 2004 paper to which the reviewers refer found that although patients who had increases in BMD had a lower fracture risk than patients showing a decrease in BMD, greater increases in BMD did not necessarily predict greater decreases in vertebral fracture risk (ref 404 Watts J Clin Densitom 2004). In addition, vertebral fracture risk was reduced in women who lost femoral neck BMD with teriparatide treatment (ref 406 Watts JBMR 2009). We have added this text on page 149.
Amgen	General: Classification of denosumab	The report classifies denosumab as a biologic agent (in contrast to pharmacologic agents), but in a number of places in the report (enumerated in the comments), the term "pharmacologic agents" is used with the clear intent to include the broader scope of agents i.e., denosumab as well as bisphosphonates, SERMs, teriparatide, and menopausal hormone therapy). It would be better simply to include denosumab in the category of pharmacologic agents.	We originally classified denosumab as a biologic agent in keeping with FDA classification. We have added text to the introduction indicating that for the purpose of this report, we will consider denosumab as a "pharmacologic agent."

Commentor and Affiliation	Section	Comment	Response
Amgen	General: Classification of denosumab	It would be preferable to classify denosumab as a RANKL inhibitor, as it is the first of what will undoubtedly become a class of agents.	We have added text to the introduction to indicate that denosumab functions as a RANKL inhibitor.
APTA	General: Hyperkyphosis	Hyperkyphosis increases fracture risk by several mechanisms.	We have added hyperkyphosis to the list.
APTA	General: Physical Activity	Physical activity decreases fracture risk as shown by the Nurse's Health Study.	The role of physical activity is considered as one of the interventions.
APTA	General: Exercise	Exercise (especially those that strengthen the back) has been widely shown to prevent falls, however spinal flexion exercises increase the risk for incident spinal fractures.	As falls, per se, are not within the scope of this update report, we focus instead on the association between physical activity and fracture.
APTA	General: Exercise	Exercise has been shown to affect BMD in numerous studies (cited).	Our scope limits us to looking at studies with fracture as the outcome.
NOF	General: Calcium and physical activity	Calcium and physical activity: NOF believes that the daily adequate intake of "calcium and vitamin D is a safe and inexpensive way to help reduce fracture risk…controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of fracture…NOF Clinician's Guide notes that "exercise may modestly increase bone density…"	We have added the citation to the NOF guidelines to the introduction where we discuss the roles of Ca, vitamin D, and exercise in lowering fracture risk
NOF	General: Adherence	Adherence: NOF agrees with AHRQ's observations on the factors that affect patient adherence and persistence, including, among others, age, prior history of fracture, the frequency of doses, the concurrent use of other medications, and adverse effects of medications that treat osteoporosis. NOF thanks AHRQ for shedding light on this important issue, and for suggesting that further research be conducted on ways to improve adherence.	No response needed.

Commentor and Affiliation	Section	Comment	Response
NOF	General: BMD Monitoring	BMD monitoring: NOF believes that "BMD testing performed in DXA centers using accepted quality assurance measures is appropriate for monitoring bone loss." Furthermore, NOF believes that there are several techniques which may be used to monitor the effectiveness of medications that treat osteoporosis, e.g., Central DXA, QCT, (but not peripheral DXA, QCT or QUS). In addition, NOF believes that "[s]erial central DXA BMD testing is an important component of osteoporosis management." NOF Clinician's Guide asserts that: "Suppression of biochemical markers of bone turnover after 3-6 months of specific antiresorptive osteoporosis therapies, and biochemical marker increases after 1-3 months of specific anabolic therapies, have been predictive of greater BMD responses in studies evaluating large groups of patients…"	The role of DXA in diagnosis is presented. Since part of the charge of this study is to examine the evidence for monitoring BMD, we have refrained from discussing this evidence in the introduction, although as the response to KQ5 notes, evidence was insufficient to determine the impact of serial monitoring. The use of markers of bone turnover is not part of the scope of the review.
Peer Reviewer 1	General	Quality of the report: Superior	No response needed.
Peer Reviewer 2	General	Quality of the report: Good	No response needed.
Peer Reviewer 4	General	Quality of the report: Good	No response needed.
Peer Reviewer 3	General	Quality of the report: Good	No response needed.
Peer Reviewer 6	General	Quality of the report: Good	No response needed.
Peer Reviewer 7	General	Quality of the Report: Fair	No response needed.
Peer Reviewer 1	General	Clarity and Usability: Yes	No response needed.
Peer Reviewer 2	General	Clarity and Usability: I like the systematic way the authors go through the questions and key issues/ideas in the area of osteoporosis. well done in this respect.	No response needed.
Peer Reviewer 4	General	Clarity and Usability: Structure is fine. Terminology should not simply be transported from Results to Executive Summary.	Unfortunately, the comment did not specify which terminology needs to be clarified.
Peer Reviewer 3	General	Clarity and Usability: These seem quite reasonable with the exceptions of those noted above.	No response needed
Peer Reviewer 7	General	Clarity and Usability: The report is structured and organized well. However, as commented earlier, the report would be more useful to inform policy and practice if a summarized effect size were presented in the key points.	Unfortunately, as we did not do meta-analyses on the efficacy findings, we cannot present summarized effect sizes.

Commentor and Affiliation	Section	Comment	Response
Peer Reviewer 7	General: Key Questions	*{Is the report clinically meaningful}* The report provides clinically meaningful information; however, as discussed below, the report could take one step further and provide better summarized informatin to aid clinical decision making. The biggest concern for the report is that the report lacks real data synthesis, and did not do any quantitative synthesis. Not that every report needs quantitative synthesis, but for this report, a combined estimate from all available trials would provide much more concrete and clear information for the audience of this report. *{Target population and audience explicitly defined}* The target population are more explicitly defined than the audience. *{Key questions appropriate and explicitly stated}* The key questions seem to be appropriate and explicitly stated.	This report is an update of an earlier CER on this topic. As such, we started with the findings of that review and then updated the search and incorporated new evidence using the framework of the original CER. That framework used existing systematic reviews of efficacy that conducted meta-analyses and then included additional trials not included in the prior analyses. It did not do de novo meta-analyses when meta-analyses already existed. There is EPC guidance on this issue: see Whitlock EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. Ann Intern Med. 2008 May 20;148(10):776-82).
Peer Reviewer 4	General: Adverse Events	The adverse events section is problematic. Only relative risk data are shown. Some RRs are quite high, but the event is quite rare. Consider adding percentages that report the AE.	We have calculated the risk differences to capture that information and have added the ones that are significant.
Peer Reviewer 4	General: GI AE's	GI AEs are higher with daily BP than weekly or monthly. Analyses should separate by daily versus other frequency.	We have now analyzed GI AEs by dosing frequency and route of administration (ROA), separately for mild and serious AEs. Because few studies compared dosing frequencies or ROAs within the same study, we have had to do indirect comparisons.