Evidence-based Practice Center Systematic Review Protocol

Project Title: Long-term Drug Therapy and Drug Holidays for Osteoporotic Fracture Prevention

Initial publication date: April 13, 2018
Amendment Date: October 5, 2018
(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Osteoporosis is a skeletal disorder of low bone mass and microarchitectural deterioration of bone, leading to bone fragility and increased risk of fracture.[1] In 1994, a World Health Organization (WHO) Study Group operationally defined osteoporosis in women as femoral neck bone mineral density (BMD) equal to or worse than 2.5 standard deviations below the average BMD of young white women.[2] Considering BMD at either the femoral neck or lumbar spine, and extrapolating this definition to men and nonwhite women, it is estimated that more than 10 million U.S. adults aged 50 years or older have osteoporosis.[3] About 2 million U.S. adults experience an osteoporotic or other low- or nontraumatic fracture each year.[4] Many types of fractures cause pain, disability and impaired quality of life, and hip and clinical vertebral fractures also are associated with an increased risk of mortality. Because risks of hip, vertebral and other fractures rise steeply with age, and because the population is aging, the absolute number of these fractures is projected to increase substantially in coming decades.

In short-term randomized controlled trials (RCTs) (18 months to 3 years), bisphosphonates, denosumab and teriparatide have lowered risk of vertebral and nonvertebral fractures, and bisphosphonates and denosumab have lowered risk of hip fractures.[5] However, evidence of fracture protection is predominately from studies of postmenopausal women with osteoporosis defined by low bone density or by the presence of vertebral fractures found on screening x-rays. In contrast, short-term drug trials generally have not shown reduced fracture risk in postmenopausal women without osteoporosis, even in those who had heightened fracture risk because of low bone mass (i.e., osteopenia) or other factors (e.g., falls, high FRAX® score[6]).[7]

The benefits of longer-term osteoporosis drug treatment are unclear. Evidence on fracture prevention from long-term RCTs is available only for bisphosphonates, and has shown that treatment of postmenopausal women with osteoporosis for 10 years vs. 5 years (alendronate) or 6 years vs. 3 years (zoledronic acid) inconsistently reduced risk of vertebral fractures, but did not reduce risk of hip or other nonvertebral fractures.[8, 9] Results of these long-term trials suggest that the benefit of continuing bisphosphonate treatment beyond 3 to 5 years wanes over time.
RCT evidence about anti-fracture effects of osteoporosis drug treatment in older men is sparse and has been considered insufficient for making treatment recommendations. A 2012 AHRQ review found that few published trials included at least half men, and that these trials were short-term, were not powered to detect fracture outcomes, and either were open-label or focused on special populations (e.g., people with cystic fibrosis).[10]

With limited data on fracture prevention from long-term treatment trials, and the high cost of trials adequately powered to evaluate incident fracture outcomes, many investigators have sought to identify appropriate surrogate endpoints. Though baseline BMD strongly predicts fracture risk, change in BMD from baseline during treatment has not consistently predicted risk of incident fracture with short-term drug treatment. Less is known about whether changes in BMD with long-term drug treatment predict fracture risk.

Osteoporosis treatment harms vary by drug class. In short-term RCTs and observational studies, oral bisphosphonates increase upper gastrointestinal symptoms, bisphosphonates and denosumab are associated with rare atypical femoral fractures and osteonecrosis of the jaw, denosumab increases risk of infection, teriparatide increases risk of hypercalcemia, raloxifene increases risk of hot flashes, and both raloxifene and estrogen increase risk of infection of venous thromboembolism and stroke.[5] Observational data suggest that the risk of atypical femoral fracture, though still rare, increases with longer-term bisphosphonate use.[11]

We are unaware of any systematic literature reviews showing whether the efficacy and harms of long-term osteoporosis drug treatment vary as a function of patient characteristics. The identification of factors that predict long-term osteoporosis drug treatment efficacy and harms may enable prescribers and patients to collectively make more informed decisions about osteoporosis drug treatment utilization over time. Potentially important modifiers of efficacy and/or harms may include patient and drug characteristics, bone imaging measures and biochemical bone turnover markers. Better understanding about predictors of treatment outcomes may allow better tailoring of osteoporosis drug treatment to maximize therapeutic benefit (e.g., reduced fracture risk) while minimizing harms.

The uncertainty about the benefits of long-term bisphosphonate use coupled with concerns that long-term bisphosphonate persistence in bone might inhibit normal bone repair of microdamage and thereby increase fracture risk[12, 13] have led to the concept of drug holidays, where treatment is temporarily discontinued with the intent of maximizing benefits and minimizing harms.[13] Though several groups advocate bisphosphonate drug holidays, there is no consensus about who should get them, when they should start, how long they should last, how they should be monitored, and the criteria for whether and what treatment to restart.[13-15]
II. The Key Questions

KQ1: Among men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass†, what is the efficacy of long-term (>3 years) osteoporosis drug therapy in reducing risk of incident fracture and on change in BMD?

KQ2: Among men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass†, does efficacy of long-term (>3 years) osteoporosis drug therapy in reducing risk of incident fracture vary as a function of patient, bone, or osteoporosis drug characteristics?
- Patient characteristics (age, sex, race, osteoporosis status*, fracture history [clinical fractures, radiographic vertebral fractures], calculated fracture risk [e.g. FRAX®], comorbid conditions)
- Bone characteristics (BMD, biomarkers)
- Osteoporosis drug characteristics (dose, frequency, treatment duration, delivery route)

KQ3: Among men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass†, what is the risk of harms associated with long-term (>3 years) osteoporosis drug therapy?

KQ4: Among men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass†, does risk of harms associated with long-term (>3 years) osteoporosis drug therapy vary as a function of patient, bone, or osteoporosis drug characteristics?
- Patient characteristics (age, sex, race, osteoporosis status*, fracture history [clinical fractures, radiographic vertebral fractures], calculated fracture risk [e.g. FRAX®], comorbid conditions)
- Bone characteristics (BMD, biomarkers)
- Osteoporosis drug characteristics (dose, frequency, treatment duration, delivery route)

KQ5: Among men and postmenopausal women aged ≥50 years currently receiving drug therapy started in the setting of osteoporosis* or osteopenia/low bone mass† to prevent fracture, what is the effect of osteoporosis drug treatment holidays on incident fracture risk and on change in BMD?

KQ6: Among men and postmenopausal women aged ≥50 years currently receiving drug therapy started in the setting of osteoporosis* or osteopenia/low bone mass† to prevent fracture, does the effect of osteoporosis drug treatment holidays on incident fracture risk vary as a function of patient, bone or osteoporosis drug characteristics?
- Patient characteristics before, during, and at the end of drug treatment holidays (age, sex, race, osteoporosis status*, fracture history [clinical fractures,
radiographic vertebral fractures], calculated fracture risk [e.g., FRAX®], comorbid conditions)

- Bone characteristics before, during, and at the end of drug treatment holidays (BMD, biomarkers)
- Osteoporosis drug characteristics (pre-drug holiday agent/class, time between drug initiation and start of drug holiday, duration of drug holiday, post-drug holiday agent/class)

KQ7: Among men and postmenopausal women aged >50 years currently receiving drug therapy started in the setting of osteoporosis* or osteopenia/low bone mass† to prevent fracture, what is the risk of harms of osteoporosis drug treatment holidays?

KQ8: Among men and postmenopausal women aged >50 years currently receiving drug therapy started in the setting of osteoporosis* or osteopenia/low bone mass† to prevent fracture, does risk of harms associated with osteoporosis drug treatment holidays vary as a function of patient, bone, or osteoporosis drug characteristics?

- Patient characteristics (age, sex, race, osteoporosis status*, fracture history [clinical fractures, radiographic vertebral fractures], calculated fracture risk [e.g. FRAX®], comorbid conditions)
- Bone characteristics (BMD, biomarkers)
- Osteoporosis drug characteristics (pre-drug holiday agent/class, time between drug initiation and start of drug holiday, duration of drug holiday, post-drug holiday agent/class)

*Osteoporosis defined by hip or lumbar spine DXA BMD T-score < -2.5, past clinical hip or vertebral fracture, or prevalent radiographic vertebral fracture.

†Osteopenia/low bone mass defined by hip or lumbar spine DXA BMD T-score < -1.0 and > -2.5.
<table>
<thead>
<tr>
<th>KQ</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Health Outcomes &amp; Harms</th>
<th>Timing</th>
<th>Setting</th>
<th>Study Design</th>
</tr>
</thead>
</table>
| **KQ 1:** Long-term treatment efficacy  
**KQ 2:** Predictors of long-term treatment efficacy | Men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass† being studied for fracture prevention treatment. | KQ 1: Osteoporosis drug treatment (see Table 2)  
KQ 2: Possible predictors of incident fractures with long-term treatment:  
*Patient characteristics:* pretreatment age (and years since menopause for estrogen-related treatments), race, sex, comorbid conditions (DM, CKD, CVD), osteoporosis status (osteoporosis*, low bone mass, normal), fracture history (clinical fractures, radiographic vertebral fractures), calculated pre-treatment fracture risk (e.g., FRAX®)  
*Bone characteristics:* pretreatment and early treatment (e.g. 1 year) imaging (L-spine, total hip & femoral neck DXA BMD) and biochemical markers (CTX, NTX, P1NP, bone-specific ALP)  
*Osteoporosis drug characteristics:* dose, frequency, treatment duration, delivery route | Placebo, active control | Final: Incident clinical fracture (any, hip, vertebral, nonhip nonvertebral, major osteoporotic fracture [MOF])  
Intermediate: Primary: Incident radiographic vertebral fracture  
Secondary: DXA BMD change  
(Will look at all of above outcomes for efficacy, but will only look at predictors for incident fracture outcomes.) | >3 yr | Any | **KQ 1 & 2:** RCT, CCT |
<table>
<thead>
<tr>
<th>KQ</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Health Outcomes &amp; Harms</th>
<th>Timing</th>
<th>Setting</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KQ 3</strong>: Long-term treatment harms</td>
<td>Men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass† being studied for fracture prevention treatment. For rare harms only: Men and postmenopausal women aged ≥50 years being studied for fracture prevention treatment regardless of baseline BMD.</td>
<td><strong>KQ 3</strong>: Osteoporosis drug treatment (see Table 2) <strong>KQ 4</strong>: Possible predictors of harms with long-term treatment will be the same as the possible predictors of incident fractures with long-term treatment detailed above for KQ 2.</td>
<td>Placebo, active control</td>
<td>See Table 2 below for class-specific harms</td>
<td>&gt;3 yr</td>
<td>Any</td>
<td>KQ 3 &amp; 4: RCT, CCT; Observational studies with contemporaneous controls that used methods to account for selection bias. ≥100 subjects for rare harms and ≥1000 subjects for other harms</td>
</tr>
<tr>
<td><strong>KQ 5</strong>: Effect of drug treatment holidays</td>
<td>Men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass currently receiving osteoporosis drug therapy for fracture prevention.</td>
<td><strong>KQ 5</strong>: Osteoporosis drug treatment holiday <strong>KQ 6</strong>: Possible predictors of incident fractures with drug holidays: <em>Patient characteristics</em>: age, sex, race, osteoporosis status*, fracture history [clinical fractures, radiographic vertebral fractures], calculated fracture risk [e.g. FRAX®], comorbid conditions <em>Bone characteristics</em>: BMD, biomarkers <em>Osteoporosis drug characteristics</em>: pre-drug holiday agent/class, time between drug initiation and start of drug holiday, duration of drug holiday, post-drug holiday agent/class</td>
<td>Continued osteoporosis drug treatment after ≥1 yr prior osteoporosis drug treatment</td>
<td>Final: Incident clinical fracture (any, hip, vertebral, nonhip nonvertebral, major osteoporotic fracture [MOF]) Intermediate: Primary: Incident radiographic vertebral fracture Secondary: DXA BMD change</td>
<td>≥1 yr osteoporosis drug discontinuation after ≥1 yr prior osteoporosis drug treatment</td>
<td>Any</td>
<td>KQ 5 &amp; 6: RCT, CCT</td>
</tr>
<tr>
<td><strong>KQ 6</strong>: Predictors of effect of drug treatment holidays</td>
<td>Men and postmenopausal women aged ≥50 years with osteoporosis* or osteopenia/low bone mass currently receiving osteoporosis drug therapy for fracture prevention.</td>
<td><strong>KQ 5</strong>: Osteoporosis drug treatment holiday <strong>KQ 6</strong>: Possible predictors of incident fractures with drug holidays: <em>Patient characteristics</em>: age, sex, race, osteoporosis status*, fracture history [clinical fractures, radiographic vertebral fractures], calculated fracture risk [e.g. FRAX®], comorbid conditions <em>Bone characteristics</em>: BMD, biomarkers <em>Osteoporosis drug characteristics</em>: pre-drug holiday agent/class, time between drug initiation and start of drug holiday, duration of drug holiday, post-drug holiday agent/class</td>
<td>Continued osteoporosis drug treatment after ≥1 yr prior osteoporosis drug treatment</td>
<td>Final: Incident clinical fracture (any, hip, vertebral, nonhip nonvertebral, major osteoporotic fracture [MOF]) Intermediate: Primary: Incident radiographic vertebral fracture Secondary: DXA BMD change</td>
<td>≥1 yr osteoporosis drug discontinuation after ≥1 yr prior osteoporosis drug treatment</td>
<td>Any</td>
<td>KQ 5 &amp; 6: RCT, CCT</td>
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<tr>
<td>KQ</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Health Outcomes &amp; Harms</td>
<td>Timing</td>
<td>Setting</td>
<td>Study Design</td>
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| KQ 7: Harms of drug treatment holidays  
KQ 8: Predictors of harms of drug treatment holidays | Men and postmenopausal women aged >50 years with osteoporosis* or osteopenia/low bone mass currently receiving osteoporosis drug therapy for fracture prevention.  
KQ 7: Osteoporosis drug treatment holiday  
KQ 8: Possible predictors of harms with drug holidays will be the same as the possible predictors of incident fractures with drug holidays detailed above for KQ 6. | Continued osteoporosis drug treatment after ≥1 yr prior osteoporosis drug treatment | See Table 2 below for class-specific harms | ≥1 yr osteoporosis drug discontinuation after ≥1 yr prior osteoporosis drug treatment | Any | KQ 7 & 8: RCT, CCT, observational studies with contemporaneous controls that used methods to account for selection bias. >100 subjects for rare harms and ≥1000 for other harms |

**Abbreviations:** ALP = alkaline phosphatase, BMD = bone mineral density, CCT = controlled clinical trial, CTX = C-terminal telopeptide, DXA = dual-energy x-ray absorptiometry, MOF = major osteoporotic fracture, NTX = N-terminal telopeptide, RCT = randomized clinical trial

*Osteoporosis defined by hip or lumbar spine DXA BMD T-score of -2.5 and worse, past clinical hip or vertebral fracture, or prevalent radiographic vertebral fracture.

†Osteopenia/low bone mass defined by hip or lumbar spine DXA BMD T-score < -1.0 and > -2.5.
Table 2. Drugs Used for Osteoporosis Treatment and Prevention

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug name</th>
<th>Delivery route</th>
<th>Dosing frequency</th>
<th>Short-term</th>
<th>Long-term</th>
<th>Class-specific harms for consideration in this evidence report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonate</td>
<td>Alendronate</td>
<td>Oral</td>
<td>Daily, weekly</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td><strong>Bisphosphonates and denosumab</strong>: Osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, heart attacks, musculoskeletal pain, upper GI intolerance, esophageal cancer</td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>Ibandronate</td>
<td>Oral, IV</td>
<td>Daily, weekly, monthly</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>Risedronate</td>
<td>Oral</td>
<td>Daily, weekly</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>Zoledronic acid</td>
<td>IV</td>
<td>Annually</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td></td>
</tr>
<tr>
<td>Biologic</td>
<td>Denosumab</td>
<td>SC</td>
<td>6 months</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (PTH) related anabolic</td>
<td>Teriparatide (recombinant PTH)</td>
<td>SC</td>
<td>Daily</td>
<td>1-2 yr</td>
<td>Not used &gt;2 yr</td>
<td>Hypercalcemia, hypercalciuria, osteosarcoma, fracture after stopping therapy, upper GI intolerance</td>
</tr>
<tr>
<td>PTH related anabolic</td>
<td>Abaloparatide (PTH analogue)</td>
<td>SC</td>
<td>Daily</td>
<td>1-2 yr</td>
<td>Not used &gt;2 yr</td>
<td></td>
</tr>
<tr>
<td>SERM</td>
<td>Raloxifene</td>
<td>Oral</td>
<td>Daily</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td>Stroke, venous thromboembolic disease (pulmonary embolism, deep venous thrombosis), hot flashes, mild cognitive impairment, dementia, mortality</td>
</tr>
<tr>
<td>Estrogen and Estrogen/ Progestin combination products</td>
<td>Multiple*</td>
<td>Oral, transdermal, transvaginal</td>
<td>Daily</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td>Cardiovascular disease (heart attack, stroke), venous thromboembolic disease (pulmonary embolism, deep venous thrombosis), cancer (breast, ovarian, endometrial, colorectal), mild cognitive impairment, dementia, mortality</td>
</tr>
<tr>
<td>Estrogen with SERM</td>
<td>Conjugated estrogens/ bazedoxifene*</td>
<td>Oral</td>
<td>Daily</td>
<td>1-3 yr</td>
<td>&gt;3 yr</td>
<td></td>
</tr>
<tr>
<td>Anti-sclerostin monoclonal antibody</td>
<td>Romosozumab†</td>
<td>SC</td>
<td>Monthly</td>
<td>1 yr</td>
<td>Not used &gt;1 yr</td>
<td>Cardiovascular disease (heart attack, stroke), osteonecrosis of the jaw, atypical femoral fracture</td>
</tr>
</tbody>
</table>

*FDA approved for osteoporosis prevention, but not for osteoporosis treatment.

†Not currently FDA approved for any indication. Will be included in this review if it receives FDA approval before the close of the draft report peer/public review comment period.

IV = intravenously, SC = subcutaneously, SERM = selective estrogen receptor modulator
III. Analytic Framework

Figure 1. Analytic Framework for Long-term Drug Therapy and Drug Holidays for Osteoporosis Fracture Prevention. This figure depicts the key questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how long-term osteoporosis drug treatment versus control and osteoporosis drug holiday versus continued treatment may result in final health outcomes of incident clinical fractures and intermediate outcomes such as incident radiographic vertebral fractures and change in BMD. It also illustrates how adverse events may occur with long-term treatment or drug holidays. Finally, it illustrates how patient, bone, and osteoporosis drug treatment characteristics may predict the effect of long-term osteoporosis drug treatment on risk for incident fractures and harms, and predict the effect of drug holidays on risk for incident fractures.

*Osteoporosis defined by hip or lumbar spine DXA BMD T-score \(-2.5\), past clinical hip or vertebral fracture, or prevalent radiographic vertebral fracture.

†Osteopenia/low bone mass defined by hip or lumbar spine DXA BMD T-score \(< -1.0\) and \(> -2.5\).
### IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

#### Table 3. Study Inclusion Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Entry Criteria</th>
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</table>
| **Study Population** | • Include:  
  ▪ Adults aged >50 years, including men and postmenopausal women  
  ▪ Participants with osteoporosis (osteoporosis defined as hip or vertebral DXA T-score ≤ -2.5, past clinical hip or vertebral fracture, or radiographic vertebral fracture) or osteopenia/low bone mass (hip or vertebral DXA T-score > -2.5 and <= -1) being treated to prevent fractures.  
  ▪ For rare harms key questions (KQ 3, 4, 7 & 8):  
    ▪ Also include participants without osteoporosis or with unknown osteoporosis status being treated to prevent fractures.  
  ▪ Exclude:  
    ▪ Studies focused on populations with known secondary causes of osteoporosis (e.g., transplant, spinal cord injury, exogenous glucocorticoids, hormone suppressive therapy, endogenous hypercortisolism, hyperparathyroidism, hyperthyroidism); though will include studies focused on populations with CKD, DM, or CVD.  
    ▪ Studies focused on patients with cancer metastatic to bone.  
    ▪ Studies focused on drug effects on acute fracture healing. |
| **Study Objectives** | • To systematically evaluate:  
  ▪ The efficacy and harms of long-term osteoporosis drug treatment (>3 years).  
  ▪ Predictors of long-term osteoporosis drug treatment on incident fractures and harms  
  ▪ The effect and harms of osteoporosis drug treatment holidays.  
  ▪ Predictors of osteoporosis drug treatment holidays on incident fractures and harms. |
| **Study Design**    | • All key questions: RCTs, CCTs  
  • For assessment of harms (KQ 3, 4, 7 & 8):  
    ▪ Also include observational studies with contemporaneous human controls that employed methods to account for selection bias (adjust for age, comorbidity, and some measure of fracture risk [e.g., past fracture, BMD or fracture risk calculator]).  
      ▪ Rare harms (i.e., AFF, ONJ, Afib): Sample size must be >100 and may include case-control, retrospective or prospective cohort, or administrative data studies.  
      ▪ Nonrare harms: Sample size must be ≥1000 and limited to prospective cohort studies.  
    ▪ All key questions: Exclude case report, case series, post-marketing reports. |
| **Interventions**   | • Drugs FDA approved for osteoporosis treatment or prevention (bisphosphonates, denosumab, teriparatide, abaloparatide, estrogen*, estrogen/progesterone*, SERM, estrogen/SERM*, romosozumab†)  
  • Discontinuation of osteoporosis drug treatment |
<table>
<thead>
<tr>
<th>Category</th>
<th>Entry Criteria</th>
</tr>
</thead>
</table>
| Comparisons | • For treatment efficacy and harms: Placebo, active contemporaneous control  
• For drug holiday: Continued osteoporosis drug treatment |
| Outcomes | • Final health outcomes: any incident clinical fracture (e.g., any, hip, vertebral, nonhip nonvertebral, MOF)  
• Intermediate health outcomes:  
  ▪ Primary: Incident radiographic vertebral fracture  
  ▪ Secondary: Change in BMD (Will assess this additional outcome only in studies that also report incident clinical or radiographic fracture outcomes, whether fractures were an efficacy outcome or a safety outcome.)  
• Harms (Serious adverse events and specific harms as listed in Table 2) |
| Outcome predictors (applicable only for KQs 2, 4 & 6) | • For KQs 2, 4, 6, and 8:  
  ▪ Patient characteristics: pretreatment age, race, sex, comorbid conditions (DM, CKD, CVD), osteoporosis status (osteoporosis, low bone mass, normal), fracture history (clinical fracture, radiographic vertebral fracture), calculated pre-treatment fracture risk (e.g., FRAX®)  
  ▪ Bone characteristics: pretreatment and early treatment (e.g. 1 year) imaging (L-spine, total hip & femoral neck DXA BMD) and biochemical markers (CTX, NTX, P1NP, bone-specific ALP)  
  • For KQs 2 and 4 only:  
    ▪ Osteoporosis drug characteristics: dose, frequency, treatment duration, delivery route  
  • For KQs 6 and 8 only:  
    ▪ Osteoporosis drug characteristics: pre-drug holiday agent/class, time between drug initiation and start of drug holiday, duration of drug holiday, post-drug holiday agent/class |
| Timing | • Long-term osteoporosis drug treatment: treatment duration >3 years.  
• Osteoporosis drug treatment holidays: treatment cessation >1 year after prior osteoporosis drug treatment >1 year |
| Setting | Any |
| Publication type | • Published in full text in peer reviewed journals.  
• Will use systematic reviews and eligible studies to identify additional references.  
• Data may be supplemented by grey literature if it includes sufficient information to assess eligibility and risk of bias. |
| Language of Publication | English |

*FDA approved for osteoporosis prevention, but not for osteoporosis treatment.
†Not currently FDA approved for any indication. Will be included in this review if it receives FDA approval before the close of the draft report peer/public review comment period.
B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Electronic database search: We will search Ovid Medline, Ovid Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials, nonrandomized controlled trials, and observational studies published and indexed in these bibliographic databases since 1995, which is the first year an RCT on osteoporosis treatment was published for any of the interventions included in this review. The search algorithm includes relevant medical subject headings and natural language terms for the concepts of osteoporosis and drug treatment and is combined with validated filters to select study designs (Appendix 2). We will supplement our electronic database search strategies with citation searches of eligible studies and citation searches of relevant systematic reviews published in 2012 or more recently that are identified in our initial electronic database search.

Grey literature search: We will search ClinicalTrials.gov to identify relevant completed studies that did not report outcomes and analyses in the published literature to help assess publication and reporting bias, and to identify and track ongoing studies that may contribute information to address the key questions in the future. To solicit Pharmaceutical Manufacturer protocols with additional information about published or unpublished drug studies, AHRQ will open a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal and send out a notification through its listserv.

We will update both the electronic database and grey literature searches while the draft report is under peer/public review.

C. Study Selection

We will review bibliographic database search results for studies relevant to our PICOTS framework and study-specific entry criteria (Table 3). References identified from these electronic databases and from citation searches of systematic reviews, peer and public review or through the SEADS portal will be pooled and deduplicated in EndNote (EndNote X7 and X8, Clarivate Analytics, Philadelphia, PA). Search results then will be downloaded into Distiller (DistillerSR, Evidence Partners, Ottawa, Canada) where they will be further deduplicated. Titles and abstracts will be reviewed by two of our six independent research staff assigned to this task to identify studies meeting PICOTS framework and inclusion/exclusion criteria. Studies considered ineligible by two of these investigators will be excluded from the review, while those considered potentially eligible by at least one of these investigators will be forwarded for full text screening. All studies forwarded for full-text screening will be independently evaluated by two of six investigators to determine if inclusion criteria are met and, if excluded, to determine the reason(s) for exclusion. Differences in screening decisions will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator. Before and throughout screening, team members will meet regularly to discuss study entry criteria, the screening process and issues as they arise to ensure consistency within and between investigators.
D. Data Abstraction and Data Management

Studies meeting eligibility criteria will be distributed among investigators for data extraction. Relevant data will be extracted into evidence and outcomes tables by one investigator and reviewed and verified for accuracy by a second investigator.

All eligible studies first will be assessed for risk of bias (see IV.E. for details of risk of bias factors). Studies determined to be high risk of bias will have only limited data extracted, most of which will have been obtained using Distiller during full text eligibility screening: author, year of publication, study design, intervention, types of efficacy/effect outcomes, and whether any adverse effects are reported.

Additional data will be extracted from studies assessed as having low to moderate risk of bias. These fields will include inclusion and exclusion criteria, setting, participant baseline characteristics (age, race, sex, comorbid conditions [DM, CKD, CVD], osteoporosis vs. osteopenia, fracture history, calculator estimated fracture risk, BMD, CTX, NTX, P1NP, bone-specific alkaline phosphatase), intervention details (drug class, name, dose and delivery route), control intervention details, follow-up duration, and results of efficacy/effect outcomes and adverse effects.

E. Assessment of Methodological Risk of Bias of Individual Studies

Based upon AHRQ guidance, we will assess each eligible study for risk of bias in its design, analysis and reporting.[18] Risk of bias will be evaluated for the outcomes of incident clinical fractures (any, hip, vertebral, nonhip nonvertebral, major osteoporotic fracture [MOF]), incident radiographic vertebral fractures, atypical femoral fractures (AFF), osteonecrosis of the jaw (ONJ), and incident clinical fracture after stopping therapy (rebound fractures). For each of these outcomes, two investigators will independently assess each study for bias in several different domains, and then, considering these assessments, also rate its overall risk of bias as low, moderate, or high. Investigators will consult to reconcile any discrepancies in risk of bias ratings for both individual domains and overall. Types of potential bias we will evaluate for each eligible study will include:

- **Selection bias**: adequacy of randomization method
- **Attrition bias**: loss to follow-up, both overall and differentially between treatment groups
- **Detection bias**: outcome assessor masking, outcome measurement quality
- **Performance bias**: intention to treat analysis, adjustment for potential confounding variables, participant masking to treatment assignment
- **Reporting bias**: selective reporting of outcomes

F. Data Synthesis

Results will be organized first by treatment comparison and then by treatment outcome (incident clinical fractures, incident radiographic vertebral fractures, change in BMD, then harms). For studies with low and moderate risk of bias, we will summarize the
results in evidence tables and synthesize evidence for each unique treatment comparison with meta-analysis when possible and appropriate. We will assess the clinical and methodological heterogeneity (participant population, intervention, outcome measures) and variation in effect size to determine appropriateness of pooling data.[19] We will synthesize data using a random effects model in RevMan.[20] We will calculate risk ratios (RR) and absolute risk differences (RD) with the corresponding 95 percent confidence intervals (CI) for binary outcomes and weighted mean differences (WMD) and/or standardized mean differences (SMD) with the corresponding 95 percent CIs for continuous outcomes. We will assess statistical heterogeneity with Cochran’s Q test and measure magnitude with $I^2$ statistic.[19] If the analyses yield substantial heterogeneity (i.e. $I^2 \geq 70\%$), we will stratify the results to assess treatment effects based on patient or study characteristics and/or explore sensitivity analysis. When data allow, we also will perform stratified analyses to evaluate a priori selected possible predictors of osteoporosis drug treatment and osteoporosis drug treatment holidays on effects and harms outcomes (i.e. age, race, sex, comorbid conditions [DM, CKD, CVD], osteoporosis status, fracture history, calculated estimated fracture risk, BMD, CTX, NTX, P1NP, bone-specific alkaline phosphatase, drug dose, treatment duration and delivery route, and follow-up duration).

G. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

Two investigators will independently assess five required domains and other possible factors to grade the strength of evidence within each treatment comparison for included studies. Differences in individual domain ratings and overall strength of evidence grades will be resolved by consultation between investigators, and, if necessary, consultation with a third investigator.

For each treatment comparison, strength of evidence will be graded for the efficacy/effect outcomes of incident clinical fracture (any skeletal site), incident hip fracture, incident nonhip nonvertebral fracture, incident MOF, and incident radiographic vertebral fractures. Strength of evidence also will be graded for the harms of serious adverse events, AFF, ONJ, and incident clinical fracture after stopping therapy (rebound fractures).

Individual strength of evidence domains will be: (1) study limitations (risk of bias); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size among studies); (4) precision (degree of certainty around an estimate); and (5) reporting bias.[21] Based on study design and risk of bias, study limitations will be rated as low, medium, or high. Consistency among studies will be rated as consistent, inconsistent, or unknown/not applicable (e.g., single study) based on whether intervention effects are similar in direction and magnitude, and statistical significance of all studies. Directness will be rated as either direct or indirect based on the need for indirect comparisons when inference requires observations across studies. That is, more than one step is needed to reach the conclusion. Precision will be rated as precise or imprecise based on the degree of certainty surrounding each effect estimate or qualitative finding. An imprecise estimate is one for which the
confidence interval is wide enough to include clinically distinct conclusions based upon established minimal detectable differences when available. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association.

Based on these elements, we will assess the overall strength of evidence for each comparison and outcome as:[21]

- **High**: Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence, findings believed to be stable.
- **Moderate**: Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low**: Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient**: No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

An overall rating of high strength of evidence would be assigned when included studies were RCTs with a low risk of bias, and the results were consistent, direct, and precise. If strength of evidence for a treatment-outcome comparison is rated insufficient based on assessment of only low to moderate risk of bias studies, we will consider evaluating eligible high risk of bias studies that address the same treatment-outcome comparison.

H. Assessing Applicability

Applicability of studies will be determined according to the PICOTS framework. Study characteristics that may affect applicability include, but are not limited to, the population (age, race, sex, presence or lack of comorbidities, country from which the study participants were enrolled), narrow eligibility criteria, and patient and intervention characteristics potentially associated with treatment response different than those described by population studies.[22]

V. References (See Appendix 1)

VI. Definition of Terms

- AFF: atypical femoral fracture
- AHRQ: Agency for Healthcare Research & Quality
- ALP: alkaline phosphatase
- BMD: bone mineral density
- BMI: body mass index (in kg/m²)
- CCT: controlled clinical trial
VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Table 4.

<table>
<thead>
<tr>
<th>Date</th>
<th>Section</th>
<th>Original Protocol</th>
<th>Revised Protocol</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/5/18</td>
<td>Key Questions, PICOTS table, Inclusion Criteria Table</td>
<td>KQ 5-6: “Among men and postmenopausal women aged ≥50 years currently receiving drug therapy started in the setting of osteoporosis* or osteopenia/low bone mass† to prevent fracture, what is the efficacy of osteoporosis drug treatment holidays on…” Efficacy also was use in several other places to refer to the outcomes of drug holidays.</td>
<td>KQ 5-6: “Among men and postmenopausal women aged ≥50 years currently receiving drug therapy (≥1 year) started for osteoporosis* or osteopenia/low bone mass† to prevent fracture, what is the effect of osteoporosis drug treatment holidays (≥1 year) on…” Efficacy was replaced with effect when referring only to drug holiday outcomes and with efficacy/effect when outcomes were referring to both long-term treatment and drug holiday outcomes.</td>
<td>Using the term ‘efficacy’ is an awkward fit for the concept of osteoporosis drug holiday given that the aims of drug holidays are “to preserve as much fracture reduction benefit as possible while minimizing harms.” “Efficacy” was replaced with “effect.”</td>
</tr>
</tbody>
</table>
VIII. Review of Key Questions

Key questions were refined by the Evidence-based Practice Center (EPC), then reviewed by AHRQ staff, the NIH/ODP Working Group and a Content Area Expert Group to assure that they addressed the clinical questions that drove the nomination of this topic. These reviews also aimed to make the key questions more explicit about the populations, interventions, comparisons, outcomes, treatment duration, settings and study designs being considered.

IX. NIH/ODP Working Group

In place of Key Informants, a NIH/ODP Working Group (including subject matter experts from NIAMS and NIA and staff from the Office of Disease Prevention) has provided input into identifying the development and refinement of the protocol. The NIH/ODP Working Group has participated in monthly calls with AHRQ staff and the EPC; provided written and verbal feedback on drafts of the Topic Refinement and draft protocol; participated with AHRQ staff, the EPC and a Content Area Expert Group in a webinar to refine the project scope; and, together with Technical Experts, completed a formal questionnaire to numerically rank, from highest to lowest priority, the different proposed key questions, interventions, efficacy/effects outcomes, and drug class-specific harms. The NIH/ODP Working Group also informed the EPC about a recently available draft USPSTF report on osteoporosis screening and short-term drug treatment thought to possibly overlap proposed key questions about predictors of short-term osteoporosis drug treatment efficacy and harms.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts identified to provide input in defining populations, interventions, comparisons, or outcomes and possibly to identify studies or databases to search. For the present project, Technical Experts were targeted to provide broad expertise and diverse perspectives pertinent to osteoporosis, endocrinology, rheumatology, women’s health, osteoporosis in men, primary care, clinical research, epidemiology, geriatrics, systematic reviews, guidelines, and complex medical patients/multimorbidity. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.
Technical Experts provided information to AHRQ, the NIH/ODP Working Group and the EPC on the important clinical and research issues pertinent to osteoporosis drug treatment, and on proposed key questions and PICOTS, both through conference calls and the above described prioritization questionnaire. Technical Experts will be given the opportunity to review the draft report during both the peer review and public review comment periods. Technical Experts will not perform analysis of any kind or contribute to the writing of the report.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers
Peer reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC will consider all peer review comments on the draft report in preparation of the final report. Peer reviewers will not participate in writing or editing the final report or other products. The final report will not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $5,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures
EPC core team members are required to disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder
This project was funded under Contract No. HHSA29032004T / HHSA290201500008I T O #4 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.
XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).
Appendix 1: Bibliography

Appendix 2: Sample Search
Osteoporosis-Fracture Prevention Search Dates: November 21, 2017

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:
--------------------------------------------------------------------------------
1 exp Osteoporosis/ (56601)
2 osteoporosis.ti. (24986)
3 Bone Density/ (53169)
4 exp Fractures, Bone/ (178905)
5 or/1-4 (249251)
6 Bone Density Conservation Agents/ (13618)
7 exp Diphosphonates/ (26164)
8 bisphosphonate*.ti. (6667)
9 alendronate.ti. (2190)
10 ibandronate.ti. (497)
11 risedronate.ti. (732)
12 zoledronic acid.ti. (1876)
13 or/7-12 (27852)
14 denosumab.ti. (998)
15 exp Anabolic Agents/ (15267)
16 teriparatide.ti. (835)
17 abaloparatide.ti. (22)
18 or/15-17 (16105)
19 exp Selective Estrogen Receptor Modulators/ (28675)
20 raloxifene.ti. (1433)
21 or/19-20 (28784)
22 Hormone Replacement Therapy/ (9611)
23 Estrogen Replacement Therapy/ (15549)
24 Estrogens, Conjugated/ (3783)
25 (conjugated adj2 estrogens).ti. (442)
26 (conjugated adj2 oestrogens).ti. (52)
27 bazedoxifene.ti. (203)
28 parathyroid.ti. (21206)
29 pth.ti. (2443)
30 24 or 25 or 26 or 27 or 28 or 29 (27047)
Romosozumab.ti. (37)
6 or 13 or 14 or 18 or 21 or 22 or 23 or 30 or 31 (124263)
5 and 32 (19473)
meta analysis as topic/ (17374)
meta-analy$.tw. (132466)
metaanaly$.tw. (1964)
meta-analysis/ (94826)
(systematic adj (review$1 or overview$1)).tw. (121503)
exp Review Literature as Topic/ (10321)
or/34-39 (237928)
cochrane.ab. (61695)
embase.ab. (65904)
(psychlit or psyclit).ab. (957)
(psychinfor or psycinfo).ab. (18590)
or/41-44 (100777)
reference list$.ab. (15891)
bibliograph$.ab. (16312)
hand search.ab. (1444)
relevant journals.ab. (1105)
manual search$.ab. (3843)
or/46-50 (36058)
selection criteria.ab. (28294)
data extraction.ab. (16712)
52 or 53 (42825)
review/ (2480829)
54 and 55 (28679)
comment/ (735829)
letter/ (1035382)
editorial/ (470175)
animal/ (6598636)
human/ (18057963)
60 not (61 and 60) (4708384)
or/57-59,62 (6336940)
40 or 45 or 51 or 56 (281525)
64 not 63 (266871)
randomized controlled trials as topic/ (123612)
randomized controlled trial/ (505454)
random allocation/ (101086)
double blind method/ (159463)
single blind method/ (27137)
clinical trial/ (553719)
clinical trial, phase i.pt. (20676)
clinical trial, phase ii.pt. (33325)
clinical trial, phase iii.pt. (15646)
clinical trial, phase iv.pt. (1673)
controlled clinical trial.pt. (100423)
randomized controlled trial.pt. (505454)
multicenter study.pt. (254739)
clinical trial.pt. (553719)
exp Clinical trials as topic/ (335805)
or/66-80 (1338507)
(clinical adj trial$).tw. (327584)
((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (169807)
placebos/ (36670)
randomly allocated.tw. (25617)
(allocated adj2 random$).tw. (28819)
82 or 83 or 84 or 85 or 86 or 87 (592975)
81 or 88 (1569425)
case report.tw. (279795)
case report.tw. (279795)
letter/ (1035382)
historical article/ (358172)
90 or 91 or 92 or 93 (1658574)
89 not 94 (1533984)
exp cohort studies/ (1866525)
cohort$.tw. (483043)
controlled clinical trial.pt. (100423)
epidemiologic methods/ (32559)
limit 99 to yr=1971-1983 (5524)
96 or 97 or 98 or 100 (2167906)
exp case-control study/ (974951)
(case$ and control$).tw. (459124)
102 or 103 (1309725)
105 65 or 95 or 101 or 104 (3860160)
106 33 and 65 (723)
107 33 and 95 (6177)
108 33 and 101 (3725)
109 33 and 104 (1519)
110 106 or 107 or 108 or 109 (8692)
111 limit 110 to animals (636)
112 limit 111 to humans (415)
113 110 not 111 (8056)
114 113 or 112 (8471)
115 limit 114 to "all child (0 to 18 years)" (541)
116 limit 115 to "all adult (19 plus years)" (276)
117 114 not 115 (7930)
118 117 or 116 (8206)
119 limit 118 to (addresses or autobiography or bibliography or biography or case reports or comment or dataset or dictionary or directory or editorial or interactive tutorial or interview or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or validation studies or video-audio media or webcasts) (389)
120 118 not 119 (7817)
121 limit 120 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)") (1684)
122 limit 121 to ("middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (1411)
123 120 not 121 (6133)
124 123 or 122 (7544)
125 limit 124 to english language (6901)
126 limit 125 to yr="1995 -Current" (6527)

***************************************
Database: Embase Classic+Embase <1947 to 2017 Week 47>

Search Strategy:

1 exp *Osteoporosis/ (58317)
2 osteoporosis.ti. (33878)
3 *Bone Density/ (22135)
4 exp *Fractures, Bone/ (160114)
5 or/1-4 (227622)
6 *Bone Density Conservation Agents/ (1590)
7 exp *bisphosphonic acid derivative/ (23518)
8 bisphosphonate*.ti. (8042)
9 alendronate.ti. (2785)
10 ibandronate.ti. (705)
11 risedronate.ti. (921)
12 zoledronic acid.ti. (2886)
13 or/7-12 (24459)
14 denosumab.ti. (1831)
15 teriparatide.ti. (1212)
16 abaloparatide.ti. (46)
17 14 or 15 or 16 (3048)
18 exp *Selective Estrogen Receptor Modulators/ (1852)
19 raloxifene.ti. (1741)
20 or/18-19 (3449)
21 *hormone substitution/ (9570)
22 *estrogen therapy/ (12439)
23 exp *conjugated estrogen/ (4654)
24 (conjugated adj2 estrogens).ti. (586)
25 (conjugated adj2 oestrogens).ti. (68)
26 bazedoxifene.ti. (327)
27 parathyroid.ti. (24501)
28 pth.ti. (3560)
29 23 or 24 or 25 or 26 or 27 or 28 (32182)
30 Romosozumab.ti. (63)
31 6 or 13 or 14 or 17 or 20 or 21 or 22 or 29 or 30 (82327)
32 5 and 31 (12350)
33 Clinical trial/ (967720)
34 Randomized controlled trial/ (482705)
35 Randomization/ (76524)
36 Single blind procedure/ (30258)
37 Double blind procedure/ (147602)
38 Crossover procedure/ (54478)
39 Placebo/ (321912)
40 Randomized controlled trial$.tw. (171939)
41 Rct.tw. (26582)
42 Random allocation.tw. (1803)
43 Randomly allocated.tw. (29202)
44 Allocated randomly.tw. (2326)
45 (allocated adj2 random).tw. (951)
46 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 (1492328)
47 Case study/ (60326)
48 Case report.tw. (370340)
49 Abstract report/ or letter/ (1042296)
50 47 or 48 or 49 (1464628)
51 46 not 50 (1452601)
52 Clinical study/ (169001)
53 exp case control study/ (139905)
54 family study/ (27182)
55 longitudinal study/ (108891)
56 retrospective study/ (601258)
57 prospective study/ (419321)
58 cohort analysis/ (336075)
59 (cohort adj stud*).mp. (217474)
60 (observational adj stud*).mp. (172157)
61 (case control adj stud*).mp. (177221)
62 (follow up adj stud*).mp. (64043)
63 (epidemiologic* adj stud*).mp. (100966)
64 (cross sectional adj stud*).mp. (282797)
65 or/52-64 (2122395)
66 51 or 65 (3372681)
67 32 and 66 (5210)
68 limit 67 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) (112)
69 limit 68 to (adult <18 to 64 years> or aged <65+ years>) (55)
70 67 not 68 (5098)
71  70 or 69 (5153)
72  limit 71 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or
    "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or
    "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine) (104)
73  71 not 72 (5049)
74  limit 73 to (abstract report or books or "book review" or chapter or conference abstract or
    "conference review" or editorial or letter or note or patent or short survey or tombstone) (1313)
75  73 not 74 (3736)
76  limit 75 to yr="1995 -Current" (3564)
77  limit 76 to english language (3174)