APPENDIX 5: CRITICAL APPRAISAL OF INDIVIDUAL STUDIES

Study Year, Country	Study Design, Setting	Study Strengths	Study Limitations
FREEDOM [18,36] 2009, 2011 International	RCT Study sites (hospital)	Patients were randomized. Baseline characteristics were balanced across treatment groups. Bisphosphonate use was prohibited within the prior 12 months, which is appropriate considering the residual effect of the drugs on the bone. Appropriate methods were used to assess trial outcomes: radiographs for vertebral fractures assessment and diagnostic imaging for clinical fractures confirmation. Analyses of efficacy were performed using an intention to treat methodology, considered a conservative approach. **External validity:** FREEDOM addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D, a recommended approach to maximize treatment effect representative of clinical practice.	Information was insufficient to allow judgment on allocation sequence and concealment. Blindness of investigators, patients, and study monitors was not addressed in the publication. Although blinding was less likely to influence objective outcomes such as BMD, it is important for subjective evaluations such as vertebral fractures assessed through radiographs. Patient withdrawal was not reported. However, high or unbalanced discontinuation may affect internal validity. Discontinuation from the study was required for patients with substantial decrease in BMD, which was more likely to happen in the placebo arm. **External validity:** Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population.
HORIZON PFT [19,29,30,33,37,38] 2007, 2008, 2010 International	RCT Study sites (hospital)	Reference to a double-blind design for blindness of investigators and patients. Patients were randomized and the allocation sequence seems adequately generated. Baseline characteristics were balanced across treatment arms. A washout period was required for patients who were previously treated with oral bisphosphonates. Appropriate methods were used to assess trial outcomes with radiographs for vertebral fractures assessment. The proportion of patients withdrawing over the trial was acceptable (16%), and appeared balanced between treatment arms. Analyses of efficacy were performed using the conservative intention to treat analysis approach.	Information was insufficient to allow judgment on allocation concealment and blinding of the evaluator to treatment groups. Concomitant use of some osteoporosis medication was allowed, which is a confoundant. However, 79% of patients did not take any medication and vertebral fractures were assessed in this population only. Reasons for discontinuation were not reported. Discontinuation from the study was required for patients with substantial decrease in BMD, which was more likely to happen in the placebo arm.

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		External validity: HORIZON PFT addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D.	**External validity:** Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population.
MORE[20,24-26,28,31,39,40] 1999, 2002, 2005, 2011 International	RCT Study sites (hospital)	Use of identical pills to address blindness of investigators and patients. Patients were randomized. Baseline characteristics were balanced across treatment arms. Appropriate methods were used to assess trial outcomes with radiographs for vertebral fractures assessment, which were performed centrally by radiologists blinded to treatment groups. Withdrawals were acceptable and seemed balanced between the placebo and the pooled raloxifene treatment arms. Some reasons for discontinuation were reported separately in a secondary publication, including patients with substantial BMD decrease. All analyses were performed using an intention-to-treat approach. Missing post-baseline data were imputed by carrying forward the last observation. **External validity:** HORIZON PFT addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D.	Information was insufficient to allow judgment on allocation sequence and concealment. Clinical fractures were assessed by questionnaire (no confirmation with diagnostic imaging mentioned). Overall discontinuation data were pooled for the two raloxifene groups; however, only the 60 mg treatment arm is relevant. In a secondary publication, withdrawals were unequal in terms of reason for discontinuation, with > 3 times more patients in the placebo group experiencing excessive BMD decrease or multiple fractures compared with raloxifene. **External validity:** Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population. Patients from one of the three treatment arms received raloxifene 120 mg daily, which exceeds the recommended dosage in Canada. This is not an appropriate comparator and as a result, these data were not extracted.
CORE[5] 2005 International	RCT Study sites (hospital)	CORE is the continuation from the MORE trial. The article indicated that all CORE participants and investigators remained blinded to treatment assignment from the beginning of MORE to the end of the CORE trial. Baseline characteristics were balanced across treatment arms. Appropriate methods were used to assess BMD.	CORE is the continuation from MORE and assessed the effect of raloxifene on breast cancer. The CORE BMD sub-study provided data with regard to change in BMD. Clinical fractures were assessed for the whole population as a secondary outcome. However, major limitations prevented the use of CORE fracture data in our review. These limitations include inadequate fracture assessment resulting in substantial underestimation of fracture rates, as well as

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		External validity: CORE addresses a clear and appropriate research question. Although the primary outcome is not relevant to the review, a BMD sub-study assessed change in BMD in a subset of the population consistent with our selection criteria.	allowing the use of concomitant additional bone-active agents such as bisphosphonates, calcitonin, hormones, and SERMs, which is a significant confoundant. Randomization was performed at the beginning of the MORE trial and only a subset of patients fulfilling specified criteria after three years of treatment were included in the CORE BMD sub-study. This is not considered effective to ensure between-group similarity, especially regarding unreported or potentially unidentified confounding factors. The proportion of patients withdrawing over the trial was not reported nor was the methodology used to perform analyses of efficacy. **External validity:** The CORE BMD sub-study provided data with regard to change in BMD. However, this is a surrogate outcome that does not always correlate with change in fracture risk. Bisphosphonates are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population.
Michalska[22] 2006 Austria	RCT Hospital clinic	Reference to a double-blind design and to the use of identical pills for blindness of investigators and patients. Patients were randomized. Baseline characteristics were balanced between the raloxifene and placebo groups. BMD was appropriately measured by densitometry. All randomized patients completed the trial. Analyses of efficacy were performed using a modified intention to treat approach to include all patients who received at least one dose of the study drug, had a baseline measurement and at least one post-treatment observation. Michalska is the only trial included in the systematic review that is not manufacturer-funded; however, medication was provided	Information was insufficient to allow judgment on allocation sequence and concealment. **External validity:** The trial evaluated change in BMD. However, this is a surrogate outcome that does not always correlate with change in fracture risk. Michalska is the only trial included in this review where bisphosphonate treatment was required immediately prior to enrolment. Long-term residual effect of the bisphosphonate is likely to prevent bone resorption and, hence, preclude BMD decrease from resuming. This leads to overestimation of the efficacy of subsequent antiresorptive treatments. In addition, the reasons for switching from a bisphosphonate to

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		by the pharmaceutical company. **External validity:** Michalska addresses a clear and appropriate research question. Patients were supplemented with calcium and vitamin D.	raloxifene, an agent known for a less marked antiresorptive effect, were not reported. Patients from one of the three treatment arms received alendronate, which was not selected as a comparator in our protocol. As a result, data from this treatment group were not extracted.
Silverman[23,41] 2008 International	RCT Study sites (hospital)	Reference to a double-blind design for blindness of investigators and patients. Patients were randomized and the allocation sequence seems adequately generated. Baseline characteristics were balanced across treatment arms. Appropriate methods were used to assess trial outcomes with radiographs for vertebral fractures assessment. Analyses of efficacy were performed using an intention to treat approach to include all patients randomized to treatment who received at least one dose of study drug and underwent vertebral radiography at baseline and at least once during therapy. **External validity:** Silverman addresses a clear and appropriate research question. The trial evaluated the incidence of fractures, a relevant clinical outcome. Patients were supplemented with calcium and vitamin D.	Information was insufficient to allow judgment on allocation concealment. Withdrawals appeared high, with 33% of patients discontinuing the study. The proportions were unequal in terms of reason for discontinuation which may potentially affect internal validity. **External validity:** Bisphosphonate are widely used and the exclusion of recent treatment with these drugs may not be reflective of the general population. Patients from two of the four treatment arms received bazedoxifene, which is not marketed in Canada. This is not an appropriate comparator and as a result, these data were not extracted.