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Abbreviated Update - Erythropoeiesis Stimulating Agents

Month/Year of Review: June 2012
Literature Search End Date: April Week 3 2012
New drugs: peginesatide (Omontys®)
Manufacturer: Affymax & Takeda Pharmaceuticals America (dossier received)

Current Status of PDL Class:

- Preferred Agents: DARBEPOETIN ALFA, EPOETIN ALFA (EPOGEN® - BRAND ONLY)
- Non Preferred: EPOETIN ALFA (PROCRIT®), PEGINESATIDE (pending review)

Research Questions:

- Does any of the new information change previous conclusions regarding effectiveness and safety of ESAs?
- Is peginesatide more effective or safer for the treatment of anemia due to chronic kidney disease (CKD) than currently available agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- For ESA treatment of CKD anemia, there is no target Hb level that is considered at less risk for death, serious cardiovascular events or stroke. Recommendations are to use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions. There are no differences in efficacy or safety between the epoetin and darbepoetin.
- For ESA treatment of chemotherapy induced anemia there is evidence of higher mortality, tumor progression and higher thromboembolic events associated ESA therapy. The majority of these trials targeted Hb targets > 12 g/dl. Both American and European updated treatment guidelines caution that ESA initiation should incorporate patient preferences for risk and benefit. The lowest ESA dose to prevent transfusion should be used. Non-responders should discontinue ESA after 6-8 weeks. There are no differences in efficacy or safety between the epoetin and darbepoetin.
- There is insufficient evidence to assess efficacy and safety of peginesatide relative to epoetin or darbepoetin.

Recommendations:

- There is no evidence of a difference in safety or efficacy between darbepoetin and epoetin and preference can be established on cost.
- Recommend listing peginesatide as non-preferred until more safety and efficacy data are available.
- Recommend modify the initial approval lengths for CKD associated anemia and chemotherapy induced anemia to 8 weeks to assess adequate response in concurrence with the Oregon Health Plan (OHP) list of covered services.
- Recommend the Health Evidence Review Commission reevaluate OHP guideline note 7. FDA labeling and current practice is 12 weeks.

Reason for Review:
In June 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the erythropoeiesis stimulating agents (ESAs). A March 2010 Provider Synergies Review was used as the evidence source.[1] Since this review, peginesatide (Omontys®) has been approved by the Food and Drug Administration (FDA) for the treatment of the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.[2] In addition, The FDA published new safety warning for the ESAs and several new systematic reviews and clinical practice guideline updates have been published.

Previous HRC Conclusions (June 2010):

- Evidence does not support a difference in efficacy/effectiveness between darbepoetin and epoetin
- Evidence does not support a difference in harms/adverse events between darbepoetin and epoetin
- Recommend inclusion of both chemical entities.
- The committee expressed concern about initiation of therapy that would increase Hb above 12.
    - PA indicated to insure oncology patients initiate with Hb < 10
    - PA indicated to insure CKD patients maintain Hb < 11 with individual patient consideration for therapy Hb > 11

Background: ESAs reduce the need for and risks of repeated transfusions. ESAs are FDA approved for reducing the need for transfusion in patients with anemia associated with chronic renal failure (both requiring dialysis and not requiring dialysis with hemoglobin < 10 g/dL) and anemia in non-myeloid cancer patients on chemotherapy. Epoetin has additional indications for anemia in zidovudine-treated HIV-infected patients and anemic patients (hemoglobin 10-13 g/dL) having elective non-cardiac, nonvascular surgery.[4] ESAs are also used off-label for ribavirin induced anemia, anemia associated with chronic heart failure and potentially other anemias. All ESAs must be used under a Risk Evaluation and Mitigation Strategy program because the use of ESA to achieve hemoglobin ≥ 11 g/dL is associated with increased risk for serious adverse events including death. There are also case reports of pure red cell aplasia which may be caused by neutralizing anti-erythropoietin antibodies.[4] Epoetin is typically dosed three times a week whereas darbepoetin is longer acting and dosed weekly. The Effective Health Care Program[3] published a comparison of epoetin and darbepoetin for managing chemotherapy induced anemia and concluded the evidence did not show a clinically significant difference in hemoglobin response, transfusion reduction and thromboembolic event. The Canadian Agency for Drugs and Technologies in Health (CADTH)[5] published a review of ESAs for CKD and found that based upon the pooled results of three moderate quality trials of 1 year comparing epoetin to darbepoetin (n=775) there were no significant differences in all cause mortality (n=670) or risk of cardiovascular death (n=160).

Methods:
A Medline literature search ending April Week 3 2012 for meta-analyses or randomized active-controlled trials (RCT's) comparing peginesatide or hermatide or erythropoietin or epoetin or darbepoetin for treatment of anemia. The Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, UpToDate, Dynamed and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for relevant systematic

reviews and RCTs. The FDA website was searched for background information from advisory committees, new indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, one FDA safety warning for ESAs was identified[6]; one general ESA review[4], one new systematic reviews[7] and one clinical guideline update[8] regarding use in CKD were identified; three systematic reviews [9 10 11] and two updated clinical guidelines[12 13 14] regarding use in oncology were identified; one systematic review[15] regarding use in HIV, and two systematic reviews[16 17] regarding use in heart failure were evaluated. No relevant published RCTs evaluating peginestatide were identified and the pivotal trial details were not located on the FDA website. ClinicalTrials.gov indicates 18 trials registered with 13 completed, 3 terminated and 2 still recruiting but no publications were provided. The dossier provided did not identify any fully published trials.

Systematic Reviews and Guidelines

CKD:

Dynamed[4] reported new Level 2 (mid-level) evidence of higher hemoglobin targets associated with increased risk of stroke, hypertension and vascular access thrombosis compared to lower targets in patients with chronic kidney disease from a systematic review[18] of 27 trials with methodological limitations and involving 10,452 CKD patients treated with ESAs. Higher hemoglobin targets were associated with an increased risk of stroke (RR 1.51, 95% CI 1.03-2.21) in analysis of 6 trials with 7,054 patients, increased risk of vascular access thrombosis (RR 1.33, 95% CI 1.16-1.53) in analysis of 8 trials with 6,844 patients and trends toward increased risk of mortality (RR 1.09, 95% CI 0.99-1.2) in analysis of 18 trials with 9,951 patients, serious cardiovascular events (RR 1.15, 95% CI 0.98-1.33) in analysis of 7 trials with 6,880 patients, and end-stage kidney disease requiring renal replacement therapy (RR 1.08, 95% CI 0.97-1.2) in analysis of 10 trials with 7,318 patients.[4]

The October 2010 Clinical Evidence[7] review of chronic renal failure treatments reported that moderate quality evidence suggests in people with anemia and chronic renal failure, ESAs do not lower cardiovascular events or mortality, or prevent or slow the progression to end-stage renal disease. However, ESAs reduce the risk of blood transfusions but increase the risk of stroke. This finding was based upon the same review noted by Dynamed.[18]

NICE updated the ESA monitoring recommendations in the guideline for "Anaemia management in people with chronic kidney disease".[8] The guide now recommends to keep the Hb level between 10-12 g/dl for adults, young people and children aged 2 years and older, and between 9.5 and 11.5 g/dl for children younger than 2 years of age but not to wait until Hb levels are outside the range before adjusting treatment (for example, take action when Hb levels are within 0.5 g/dl of the range's limits).[8] It is also recommended to consider accepting Hb levels below the agreed range if: high doses of ESAs are required to achieve the response or the response is not achieved despite escalating ESA doses.[8] People with anemia of CKD should be considered resistant to ESAs when: the desired Hb is not achieved despite treatment with $\geq$300 IU/kg/week of subcutaneous epoetin or $\geq$ 450 IU/kg/week of intravenous epoetin or 1.5 micrograms/kg/week of darbepoetin, or there is a continued need for the

administration of high doses of ESAs to maintain the desired Hb.[8] Previous recommendations indicate there is no evidence of a clinical difference between epoetin and darbepoetin.[8]

Oncology:

A meta-analysis[9] of survival and other safety outcomes of ESA use in oncology related anemia found no effect on mortality (60 studies: OR 1.06; 95% CI: 0.97–1.15) or disease progression (26 studies: OR 1.01; 95% CI: 0.90–1.14). There was in increased risk of venous-thromboembolic events (44 studies: OR 1.48; 95% CI: 1.28–1.72). The effect on transfusion requirements and quality of life was not investigated. This review was systematic in approach and modeled a previous Cochrane review[19] methods but failed to explicitly quality assess the studies.

The Cochrane review was updated in 2009[10] and the authors concluding that ESA treatment in cancer patients increased mortality and worsened overall survival. For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded. A total of 13,933 cancer patients from 53 trials were analyzed. ESAs were associated with mortality (HR1.17; 95% CI 1.06-1.30) and worsened overall survival (HR 1.06; 95% CI 1.00-1.12), with little heterogeneity between trials.

A CADTH[11] review confirmed the Cochrane finding but also reported treatment with ESAs prevented transfusions, compared with treatment with no ESA (RR: 0.64 [95% CI 0.56 to 0.73]), but led to an increased risk of thrombotic events (RR 1.69 [95% CI 1.27 to 2.24]) and serious adverse events (RR: 1.16 [95% CI 1.08 to 1.25]).

The AHRQ has published a protocol in June 2010[20] to address the conflicting results from the most recent meta-analyses cited above as well as two previous published in 2009.[21] [22] No estimated completion date is provided.

The American Society of Clinical Oncology and the American Society of Hematology have jointly published updated guidelines on the use of ESAs in adult cancer patients.[12] [13] New recommendations include:

- Clinicians should discuss potential harms (e.g. thromboembolism, shorter survival) and benefits (e.g., decreased transfusions) of ESAs and compare these with potential harms (e.g. serious infections, immune-mediated adverse reactions) and benefits (e.g. rapid Hb improvement) of RBC transfusions for patients undergoing myelosuppressive chemotherapy who have hemoglobin < 10 g/dL.
- If used, ESAs should be administered at the lowest dose possible and should increase Hb to the lowest concentration possible to avoid transfusions. Available evidence does not identify Hb 10 g/dL either as a threshold for initiating treatment or as a target for ESA therapy.
- ESAs should be discontinued after 6 to 8 weeks in nonresponders.
- ESAs should be avoided in patients with cancer not receiving concurrent chemotherapy, except for those with lower risk for myelodysplastic syndromes.
- Caution should be exercised when using ESAs with chemotherapeutic agents in diseases associated with increased risk of thromboembolic complications.

The European Society for Medical Oncology published clinical practice guidelines for ESAs in the treatment of anemia in cancer patients.[14] Levels of Evidence [I–IV] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology. Relevant recommendations are:

- There is no difference between different ESAs in relation to effectiveness and safety [Evidence Level I].
- Indicated for chemotherapy-induced anemia in adults with non-myeloid malignancies to prevent transfusions and improve health related quality of life. Patients not treated with chemotherapy there is no indication for the use of ESAs and there might be an increased risk of death when targeting Hb of 12-14 g/dl (Evidence Level I, A)
- The influence of ESAs on tumor response and overall survival in anemic cancer patients remains unclear. Several randomized trials have demonstrated decreased survival times and poorer regional control or progression-free survival but the design of these studies was aimed at Hb levels of >12 g/dl and included patients with a baseline Hb level of >11 g/dl [Level II].
- Consider ESA at a Hb of $\leq$ 10 g/dl to increase to < 2 g/dl or to prevent further decline (Evidence Level II,A)
- In patients with low-risk myelodysplastic syndromes based on bone marrow blast percentage, number of cytopenias and cytogenetic analysis, ESAs [+/- granulocyte-colony stimulating factor (G-CSF)] can be used to improve anemia (Evidence Level II).
- The relative risk of thromboembolic events is increased by 67% in patients treated with ESAs compared with placebo (RR 1.67; 95% CI 1.35–2.06) [Evidence Level I]. The use of ESAs should be carefully reconsidered in patients with a high risk of thromboembolic events.

HIV:

A Cochrane review[15] found evidence that epoetin compared with placebo does not reduce mortality, does not reduce transfusion requirements, did not increase hemoglobin levels, and did not improve quality of life in HIV-infected patients with anemia. The results were based on six RCTs with high risk of bias and the evidence was graded "very low". Despite this, the authors recommend epoetin for treating anemia in patients with AIDS is not justified. HIV anemia treatment guidelines are dated and still recommend epoetin.[23]

Heart Failure:

Two meta-analyses of 9 of the same RCTs and evaluating the use of ESAs for anemia associated with chronic heart failure were identified.[16] [17] This indication is an off-label use. The Cochrane review[17] was based upon 11 small RCTs and concluded ESA treatment may improve exercise tolerance, reduce symptoms, and have benefits on clinical outcomes in anemic patients with heart failure. The other review[16] concluded ESAs are associated with a decrease in CHF-related hospitalizations and improved quality of life and exercise tolerance. Neither review was able to evaluate mortality.

FDA warnings:

On June 24, 2011 the FDA modified recommendations for more conservative dosing of ESAs for patients with CKD and the manufacturers have revised the Black Box Warning.[6] In controlled trials, CKD patients experienced greater risk of death, serious cardiovascular adverse events and stroke when targeting a hemoglobin level of > 11 g/dl.[6] Labels now do not recommend a target level because no trial has demonstrated an optimal

hemoglobin level. Previously the label recommended a target hemoglobin range of 10-12 g/dl.[6] The label now recommends to individualize dosing and use the lowest dose of ESA sufficient to reduce the need for red blood cell transfusions.[6]

New Drug Evaluation- Peginesatide:

FDA approved indications: It is indicated for the treatment of anemia due to CKD in adult patients on dialysis.[2]

Potential Off-label Use: It is not for use in CKD patients not on dialysis, in patients with cancer, or as a substitute for RBC* transfusions in patients who require immediate correction of anemia.[2] A phase I[24] and phase II[25] were identified as well as very small (n=14) open-label trial evaluating use in patients with pure red-cell aplasia.[26]

Clinical Efficacy & Safety Data:

No published RCTs were identified evaluating the peginesatide. The dossier references the FDA materials, posters, abstracts and file data. The FDA approved this drug based upon two randomized, active-controlled, open-label, multi-center trials in 1,608 patients with CKD on dialysis.[27]

The FDA reviewer presentation describes four active control trials. [28] Studies AFX01-12 and AFX01-14 were conducted in 1,608 patients on dialysis and previously received epoetin. Hemoglobin levels at study entry and target levels were generally higher than what is currently recommended in the ESA labeling. In terms of change in hemoglobin at week 29-36, the primary endpoint, peginesatide was found to be non-inferior to epoetin. The safety outcomes were similar for both products but the FDA reviewer noted that patients were initially stabilized on epoetin before the study. [28] Studies AFX01-11 and AFX01-13 were in CKD patients who were not on dialysis or ESA therapy the previous three months and were iron replete. Patients were randomized 1:1:1 on peginesatide 0.025mg/kg or 0.04mg/kg every four weeks, or darbepoetin 0.75mcg/kg every two weeks. Peginesatide was found to be non-inferior to darbepoetin. However, in these studies, there was a higher rate of the adverse event composite endpoint for peginesatide (22%) vs. darbepoetin (17%) (HR 1.32 90% CI 1.02 -1.72). The primary components driving this were major adverse cardiac events. [28]

It carries the same black box warning as the other ESAs.

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY: Peginesatide is a synthetic pegylated dimeric erythropoietin receptor activating peptide that is chemically unlike erythropoietin.[28] *In vitro*, it binds to and activates the human erythropoietin resceptor and stimulates erythropoiesis in human red cell precursors.[2]

PHARMACOKINETICS[2]

Parameter	Result
SQ Bioavailability	46%, Cmax at ~48 hours
Protein Binding	Not reported
Elimination	Urinary excretion predoinates
Half-Life	IV: 25 ± 7.6 hours SQ: 53 ± 17.7 hours
Metabolism	Not metabolized

DOSE & AVAILABILITY[2]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
Single use PF vials: 2mg/0.5ml 3mg/0.5ml 4mg/0.5ml 5mg/0.5ml 6mg/0.5ml Single use PF syringes: 1mg/0.5ml 2mg/0.5ml 3mg/0.5ml 4mg/0.5ml 5mg/0.5ml 6mg/0.5ml Multiple use vials: 10mg/ml 20mg/2ml	IV or SQ	Every 4 weeks	Initial: 0.04mg/kg See labeling for conversion from epoetin or darbepoetin	None	None	Not studied	No Adjustment	Must be refrigerated and protected from light. Must be discarded after 30 days if stored between 47 and 77 degrees. Multiple use vials should be discarded after 28 days after first use.

PF=preservative free

DRUG SAFETY[2]

Serious (REMS, Black Box Warnings, Contraindications): Carries ESA Black Box Warning ESAs regarding the increased risk of death, myocardial infarction , stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. It is contraindicated in patients with uncontrolled hypertension.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Drug Name	Lexi-Comp	ISMP	Clinical Judgment
peginesatide	pegaptanib, pegaspargase, pegfilgrastim, peginterferon, pegvisomant	None	
Omontys®	None	None	Omnipen, Omnihib, Omniprope

Special populations:

It has not been studied in nursing mothers, pregnant women or children. It is in FDA Pregnancy Category C.

Tolerability:[2]

Table 3 Adverse Reactions Occurring in ≥10% of Dialysis Patients treated with OMONTYS

Adverse Reactions	Dialysis Patients Treated with OMONTYS (N = 1066)	Dialysis Patients Treated with Epoetin (N = 542)
Gastrointestinal Disorders		
Diarrhea	18.4%	15.9%
Nausea	17.4%	19.6%
Vomiting	15.3%	13.3%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	18.4%	19.4%
Cough	15.9%	16.6%
Injury, Poisoning and Procedural Complications		
Arteriovenous Fistula Site Complication	16.1%	16.6%
Procedural Hypotension	10.9%	12.5%
Nervous System Disorders		
Headache	15.4%	15.9%
Musculoskeletal and Connective Tissue Disorders		
Muscle Spasms	15.3%	17.2%
Pain in Extremity	10.9%	12.7%
Back Pain	10.9%	11.3%
Arthralgia	10.7%	9.8%
Vascular Disorders		
Hypotension	14.2%	14.6%
Hypertension	13.2%	11.4%
General Disorders and Administration Site Conditions		
Pyrexia	12.2%	14.0%
Metabolism and Nutrition Disorders		
Hyperkalemia	11.4%	11.8%
Infections and Infestations		
Upper Respiratory Tract Infection	11.0%	12.4%

Appendix 4: Quality Assessment and evidence grading methods:

The methodology and tools described below is the standard approach that will be used by OSU staff to review drugs for the Oregon Health Authority Pharmacy and Therapeutics (P&T) Committee. These methods and tools were developed by the Oregon Evidence-based Practice Center Drug Effectiveness Review Project (DERP) and used in their systematic review process. The full Review Methods for the DERP can be found on their website at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm. These methods will evolve to best fit the needs of the P&T Committee and to stay current with the standards of evidence review and principles of best evidence.

Quality Assessment

Trials included in reviews for drugs will be assessed for internal validity using the quality assessment tool below. Each trial will subsequently be rated as Good, Fair, or Poor. Studies rated as good meet all the criteria and studies that have a fatal flaw are rated poor quality. The remainder will be rated in the Fair category.

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.
3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Clinically important differences
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics. For crossover design, only reported baseline characteristics of the overall group.
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.

• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), nonadherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Grading the strength of the evidence:
The evidence will be graded as high, moderate, low or insufficient and use an approach also accepted by the Evidence-based Practice Center Program. A comprehensive evaluation will assess the major domains including are risk of bias, consistency, directness, and precision of the evidence. After assessing each of the domains for the group of studies, an overall assessment is made for each measured outcome being assessed for benefit and harm. When there is no evidence available or the evidence is too limited or too indirect to make conclusions, the evidence will be described as insufficient. The following table provides the definitions adopted by the Evidence-based Practice Center for these terms.

Strength of Evidence Grades and Definitions[1]:

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit the estimation of an effect.

References:
Oregon Evidence-Based Practice Center. Drug Effectiveness Review Project: Systematic Review Methods and Procedures. Available at: http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/upload/DERP_METHODS_WEB_Final_January-2011-2.pdf