Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis*

Draft review available for public comment from July 1, 2012 to July 30, 2012.

Research Review Citation: Lee S, Coleman CI, Limone B, Kaur R, White CM, Kluger J, Sobieraj DM. Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis. Comparative Effectiveness Review No. 85. (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I.) AHRQ Publication No. 12(13)-EHC144-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 1	General	General comments: yes	Noted, thank you.
	Introduction	Good	Noted, thank you.
	Methods	Very good	Noted, thank you.
	Results	Very good	Noted, thank you.
	Discussion/ conclusion	Very good	Noted, thank you.
	Clarity/ usability	Very good	Noted, thank you.
Peer Reviewer 2	General	Quality of the Report: Good	Noted, thank you.
		The report is meaningful. I wonder why the RCT on Briakinumab versus Methotrexate for Psoriasis has not been included even if Briakinumab is not being launched in the market	Thank you for this comment. While the RCT comparing briakinumab versus methotrexate (Reich et al 2011) was captured in our literature search, only studies that evaluate interventions and comparators with a current indication approved by the U.S. Food and Drug Administration (FDA) can be included as per AHRQ. Reich K, Langley RG, Papp KA, et al. A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis. *N Engl J Med*. 2011;365(17):1586-96.
	Introduction	Adequate	Noted, thank you.
	Methods	I wonder why the RCT on Briakinumab versus Methotrexate for Psoriasis has not been included even if Briakinumab is not being launched in the market	Thank you for this comment, please see the reply above.
	Results	The presentation and wording should be modified if the authors have not sufficient reasons to exclude the RCT on Briakinumab versus Methotrexate for Psoriasis	Thank you for this comment, please see the reply above comment.
	Discussion/Conclusion	Yes but some minor points are already partly answered in the RCT on Briakinumab versus Methotrexate for Psoriasis	Thank you for this comment. Please see the reply above.
	Clarity and Usability	Yes	Noted, thank you.
Peer Reviewer 3	General	Quality of the Report: Good	Noted, thank you.

Commentator & Affiliation	Section	Comment	Response
		General comments about the approach and discussion on short-term versus long-term efficacy and safety results. Be careful here. I would say it is impossible to compare drugs over the long-term because if a given drug is not working at 12 or 16 weeks, then it is stopped. If therapies are not working by 12-16 weeks, they will not work later. In practice and in trials, patients are not continued on therapies that do not work after this period of time. In the former, practitioners move to another therapeutic choice and in the latter, study subjects drop out of studies where drugs are not working. It should be acknowledged that it is commonplace for dermatologists to compare 12-week response rates (compared to placebo) from different studies that have very similar inclusion/exclusion criteria and design. In fact, almost all biologic trials are placebo-controlled and are similar, if not exact, in design.	Thank you for this comment. Although therapies may be stopped after 12 to 16 weeks in patients who fail treatment, there are patients who are on these therapies much longer than 16 weeks when therapies are successful. For this reason, it is also important to capture long-term safety to obtain a global aspect of how these therapies impact patient care, both benefits and harms.
		Long-term safety is not ever going to captured through comparative effectiveness trials, but instead through long-term registry data (e.g., PSOLAR).	Thank you for this comment. Although the report suggested RCT or observational studies, we have added specifically, registry studies, as you have suggested under the section of research gaps and future research needs
		To me, non-biologic therapies are “20th century medicine” and biologic therapies are “21st century medicine.” Unlike the old drugs, the newer therapies are based on advances in the basic understanding of the immunology of psoriasis. It’s almost like comparing apples and oranges. One can perform the proper comparative effectiveness studies to show superiority of the newer medicines, but most dermatologists who stay current in their practices, know already that these medicines offer significant advantages over older medicines in terms of efficacy, safety, and convenience. Thus, I fear that if researchers (and NIH) take your Research Gaps message to heart and spend considerable energy, time, and money into the proper comparative effectiveness studies, the information gleaned after many years of research may be passé. The practice of dermatology may have already moved forward with the everyday use of biologic therapies for psoriasis, knowing that the advantages are clear based on experience, patient feedback, and existing data from the placebo-controlled studies. The more clinically relevant comparisons in the future will likely be among the biologic therapies. I would incorporate these important concepts and concepts into the Discussion.	Thank you for this comment. The scope of this report was to focus on between class comparisons at the individual drug level, rather than within class comparisons, although those may also be of importance to decision makers. Therefore, the future research needs are in context of this identified scope. Without having reviewed the literature on within class comparisons, we are not in a position to make judgments as to which is of higher priority at this time. We have reviewed the report to be sure we have not suggested between class comparisons are priority over other research areas within psoriasis, such as those you have suggested (within class comparisons).

Commentator & Affiliation	Section	Comment	Response
		Efficacy, safety, and convenience are the three criteria most important when selecting a given therapy. Etanercept is 64 shots in the 1st year, adalimumab is 28 shots in the 1st year, and ustekinumab is 5 shots in the 1st year of therapy. Thus, ustekinumab is by far the most convenient therapy. On the other end of the spectrum is phototherapy, which requires 2-3 visits to the doctor's office each week. My point in mentioning convenience is that if future comparative effectiveness trials show that phototherapy (high number of visits) or etanercept (high number of shots) is favorable, patients may balk at the idea of using markedly less convenient drugs to treat their chronic disease.	Thank you for this comment. The goal of comparative effectiveness review is to compare the benefits and harms in total for the given therapies. The conclusions made are solely based on the identified data. In the end, decisionmakers are given the information that is identified in the literature to make best choices in patient care. If a report were to show improve efficacy with a less convenient therapy that would be a decision that the patient and clinician would have to make considering all evidence.
	Introduction	Psoriasis does not typically go "into remission." Dermatologists don't use this term when speaking of psoriasis.	Thank you for this comment; we have changed the terminology used to "clearance" as suggested by another reviewer.
		Tumor necrosis "factor" and not "factors."	Thank you we have fixed the error.
		Alefacept is no longer available; Astellas pulled the drug from the market in December 2011.	Thank you for this comment. Although alefacept was voluntarily withdrawn from the market by the manufacturer this year, the drug was approved and available for sale in the US while we conducted the literature search and wrote this report. However, to reflect that it is no longer being sold in the US, we have clarified this in our introduction.
		Biologics are called "biologics" because they are made through culture of cell lines, but they are not, as a whole, considered a "class" of drugs, just as non-biologics for psoriasis are not considered a "class" of drugs either. Yes, etanercept, infliximab, and adalimumab are a "class:" TNF blockers. Ustekinumab, however, is not in this class; it has a very different MOI. The non-biologics are all of a very different nature too (widely varying MOI's), so they are not a "class."	Thank you for this comment. We have added the terms biologic and nonbiologic to our glossary with a listing of the drugs which we are considering in each of these groups.
		The referencing is off and needs to be adjusted.	Thank you for this comment, we have reviewed the referencing and corrected any discrepancies that were found.
	Methods	Same comments about the use of the word "class" applies here as well.	Please see the reply above.
		"major" and not "ajor."	Thank you. We have fixed this error.
		"U.S. FDA" and not "U.S FDA." Other places in paper, say "U.S. and not "US."	Thank you, we have fixed this error.

Commentator & Affiliation	Section	Comment	Response
	Results	At the very least, this prominent publication should be mentioned in the discussion: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis.Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group. N Engl J Med. 2010 Jan 14;362(2):118-28.	Thank you for this comment and the reference you provided. Although we recognize the availability of comparative data between ustekinumab and etanercept, the inclusion criteria allows only for comparison between 1) biologics and nonbiologic systemic agents or 2) biologics and phototherapy. Therefore, discussing information regarding within class comparisons is outside of the scope of this project.
		Other missing papers of note: Efficacy of biologics in the treatment of moderate to severe psoriasis: a network meta-analysis of randomized controlled trials. Reich K, Burden AD, Eaton JN, Hawkins NS. Br J Dermatol. 2012 Jan;166(1):179-88. doi: 10.1111/j.1365-2133.2011.10583.x. Epub 2011 Nov 11.	Thank you for this comment and the reference you provided. The scope of this comparative effective review is between 1) biologics and nonbiologic systemic agents or 2) biologics and phototherapy. The study by Reich et al 2012 examines the comparative efficacy among different biologic agents using a network meta-analysis. Thus, comparisons among different biologic agents precludes this study from being included.
		Dermatologist preferences for treatments to compare in future randomized controlled comparative effectiveness trials for moderate to severe psoriasis. Wan J, Abuabara K, Troxel AB, Shin DB, Van Voorhees AS, Bebo BF Jr, Krueger GG, Callis Duffin K, Gelfand JM. Arch Dermatol. 2012 Apr;148(4):539-41.	Thank you for this comment. The scope of this report was to focus on between class comparisons on an individual drug level, rather than within class comparisons, although those may also be of importance to decision makers. Therefore, the future research needs are in context of this identified scope. Future research needs are those priorities that are identified from the results of the current report. Without having reviewed the literature on within class comparisons, we are not in a position to make judgments as to the priority of between vs. within class comparisons. We have reviewed the report to be sure we have not suggested between class comparisons are priority over other research areas within psoriasis, such as those you have suggested (within class comparisons).

Commentator & Affiliation	Section	Comment	Response
		Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. Gelfand JM, Wan J, Callis Duffin K, Krueger GG, Kalb RE, Weisman JD, Sperber BR, Stierstorfer MB, Brod BA, Schleicher SM, Bebo BF Jr, Troxel AB, Shin DB, Steinemann JM, Goldfarb J, Yeung H, Van Voorhees AS. Arch Dermatol. 2012 Apr;148(4):487-94.	Thank you for this comment and the reference you provided. The study by Gelfand et al 2012 was captured in our literature search update and was incorporated in our data synthesis.
	Discussion/Conclusion	As mentioned above, don't say "complete remission;" instead, say "complete clearance." Remission, by definition, normally implies spontaneous resolution of disease off medications.	Thank you for this comment, we have changed the terms used as suggested.
		In several places, use the word "that" instead of the word "which" unless you choose to place a comma before the word "which."	Thank you for this comment. We have reviewed the report for the use of that vs. which, as suggested.
		Why doesn't the mixed treatment comparison data include ustekinumab?	We did not conduct a mixed treatment comparison ourselves. We did however include results from previously conducted mixed treatment comparisons if they compared therapies which were comparisons of interest in this report. The mixed treatment comparison by Bansback which you are referring to was published in 2009 and the literature search was through 2007 and is likely why ustekinumab data was not captured in their analysis.
		Throughout paper, don't say "PASI score;" say "PASI," since the word "index" substitutes for the word "score."	Thank you, we have corrected the use of PASI throughout the report.
		See general comments above for additional things to consider including in the Discussion.	Noted, thank you.
	Clarity and Usability	Well organized and well-written.	Noted, thank you.
Peer Reviewer 4	General	Quality of the Report: Superior	Thank you for this comment.
		This report was very well written and achieved its stated goals. The key questions were appropriate and explicitly stated. The target population and audience are explicitly defined. It is certainly instructive to know the huge gaps in the literature preventing direct comparisons between systemic therapies.	Thank you for these comments. We worked hard to generate a report that met these facets.
	Introduction	Very clear.	Noted, thank you.
	Methods	The inclusion and exclusion critieria are justifiable. The search strategies are logical. The definitions for the outcome measures are appropriate. I cannot comment on the statistical methods.	Noted, thank you.

Commentator & Affiliation	Section	Comment	Response
	Results	The greatest strength of this paper is the detailed information in the Results section, especially as there were very few studies allowing direct comparison of systemic agents. It is certainly useful to have a comprehensive analysis of the existing literature of the systemic agents. I am not aware of any overlooked studies	Thank you for these comments. We would like to thank the reviewer for the complementary thoughts.
	Clarity and Usability	The report is well structured and organized. and the main points are clearly presented. The scope of the conclusions, however, are too limited to inform policy and practice decisions.	Thank you for these comments. The conclusions of the report are reflective of data identified through the systematic review process. Although a lack of data may be perceived as a weakness, it highlights the need for future research in an area that is important to decision makers.
Peer Reviewer 5	General	Quality of the Report: Good	Noted, thank you.
		The report comparing systemic biologic and non-biologic agents and phototherapy for plaque psoriasis uses systematic review methods and appears well done. Unfortunately, there does not seem to be very much comparative evidence from clinical trials or observational studies. Note that throughout the report there a anumber of typos. For example, page ES-11, line 34 should be 'consistent' not 'consist'.	Thank you for these comments. Typographical errors were corrected throughout the report.
	Introduction	No comment, seems to be an adequate introduction to plaque psoriasis and treatment options.	Noted, thank you.
	Methods	The methods used in the systematic review appear good. Inclusion and exclusion criteria for the review are comprehensive and cover the key criteria for locating relevant information and publications. The outcome measures cover the main clinical and patient reported endpoints used in psoriasis clinical trials. No statistical analysis was performed given the paucity of available studies.	Noted, thank you.
	Results	The amount of detail provided in the results section is adequate.	Noted, thank you.
		My only real issue was the repetitive nature of the results section where many sentences were repeated vebatim throughout the text.	Thank you for your comment. Given the size of the report, we tried to apply standard processes to make the report more readable and consistent.
		The characteristics of the included studies are adequately described in the text and appendix tables.	Noted, thank you.

Commentator & Affiliation	Section	Comment	Response
		Several of the observation studies included seem very small and poorly designed and do not provide very much evidence on comparative effectiveness.	Thank you for this comment. The quality of most observational studies was poor in nature and this impacted the strength of evidence grading since risk of bias is one of the four domains used. The poor quality of included studies is reflected by predominance of insufficient to low strength of evidence in this report.
		I think that no studies were overlooked.	Noted, thank you.
		On page 28, line 41, the heading is incorrect, should be 'alefacept'.	Thank you. We have made the change.
		On pages 12 and 13, the reference citations seem to be mixed up a bit.	Thank you, we have reviewed the references and have made sure the correct references are reflected.
	Discussion/Conclusion	The discussion and conclusion provide a good summary of the available evidence comparing biologics and non-biologic sytemic therapies.	Noted, thank you.
		The authors note that there many more placebo controlled studies, and one wonders whether these data could assist in a least further documents (in an indirect way) the outcomes and safety of the biologic agents.	Thank you for this comment. When comparing two active therapies, direct evidence is used when it is available, instead of making indirect comparisons. However, that does not preclude future research from using indirect evidence (inclusion of placebo controlled trials) to assist in making inferences about direct comparisons.
		The main findings of the review and available evidence are clearly described, and future research needs are clearly delineated.	Thank you for your comment.
	Clarity and Usability	Based on my review, the report is well designed and organized.	Thank you for your comment.
		It is a bit repetitive in places, but this seems unavoidable.	Thank you for your comment. Given the size of the report, we tried to apply standard processes to make the report more readable and consistent.
		The conclusions are clear and may inform health policy, but the paucity of studies makes it difficult to make any major conclusions. For clinical decision-making, nothing really new is described but again this is due to the lack of evidence comparing the treatments.	Noted, thank you.
Peer Reviewer 6	General	Quality of the Report: Good	Thank you.
		This is a good review of the scant literature available for the comparative treatment of chronic plaque psoriasis.	Thank you.
		The target population is stated and probably most useful to researchers given the lack of data.	Noted.

Commentator & Affiliation	Section	Comment	Response
		The key questions are appropriate and explicit, but easy to get lost in the acronyms.	Thank you for this comment. In order to enhance the readability of the report, which is already large and comprehensive, acronyms were spelled out with first mention as *AHRQ publishing guideline*. In addition, full list of acronym can be found in Appendix I. Glossary and Appendix J. Abbreviations.
		In general the details under each key questions could use a little more synthesis, perhaps stating meaningful clinical differences up front in the key points.	Thank you for this comment. Key points are used to highlight statistically significant findings as well as those with strength of evidence ratings and are not intended to synthesize data to that level of details. Instead, we utilized the discussion section to further expand on these findings as well as meaningful clinical differences.
	Abstract	Line 16, From inception-is unclear. State the exact date	Thank you for this comment. Inception is the term we describe the origination date of all databases since there is such variability in those dates. Regardless, our inclusion criteria excluded all studies before 1975.
	Executive Summary	Background has a good introduction to the problem and scope of chronic plaque psoriasis and standard recommended guidelines. The biologic agents are introduced.	Thank you.
		Suggest specifically mentioning the nonbiologic drugs.	Thank you for this suggestion. We have added the terms biologic and nonbiologic to the glossary where the specific drugs considered in each category are listed.
		A pictoral framework of the key questions would be helpful to follow the intermediate, long term outcomes and harms.	Thank you for this comment. Please refer to Figure 1 of the main report for the analytic framework which pictorially describes the information you have requested.
		A head to head trial is mentioned on ES-2 line 12, recommend mentioning the results.	Thank you for this comment. The trial referred to is included in our systematic review (CHAMPION trial) and the results are very extensively described throughout the report.

Commentator & Affiliation	Section	Comment	Response
		The key questions are explicity stated. For inclusion/exclusion criteria, were data obtained from drug manufacturers?	Thank you for this comment. As is stated in the methods section of the ES and main report: "The Scientific Resource Center of the AHRQ Effective Health Care Program contacted the manufacturers of identified interventions and comparators for scientific information packets. The same inclusion/exclusion criteria applied to the database searches were applied to packets that were received and relevant citations were manually added to the literature base."
		Results of literature search may flow better before ES1 results. For Key Question 1,2,3 headings starting on ES-7-recommend briefly noting what the KQ is asking. For KQ 1, what does this patient population look like? Are they naïve to both drugs (mtx, adalimumab, etanercept?)	Thank you for this suggestion. We have reversed the order of the results table and the literature search results in the ES as suggested. The KQ are presented early on in the ES on ES-2.
	Introduction	Good succinct background on psoriasis, the biologic agents. Nonbiologic systemic therapies are mentioned as a class, but would be good to spell out what these are (methotrexate, etc). More information about each of the drugs and phototherapy would be helpful.	Thank you for this comment. We have added 3 tables to the introduction which provide more details about the therapies included in this report.
		P3 key questions are in a difference font.	Thank you for this observation. The font and styles used throughout the report are standards set by AHRQ.
		Key questions- lots of acronyms for measures. Would be good to spell out initially (some are in the kq itself, some are not), define somewhere here or in appendix. Do the acronyms need to be in the kq; it makes for a harder read? Consider defininig later what measures are included in intermediate outcomes and final outcomes for example.	Thank you for raising your concern. We follow the AHRQ publishing guide when putting together the report.
	Methods	Inclusion and exclusion criteria were justifiable. May want to say a little more why studies before 1975 are irrelevant.	Thank you for this comment. Together with the Technical Expert Panel assembled for this project, we agreed that data prior to 1975 was not likely available for any of the included drugs and by using this cut-off date we would be safe in making the search more specific without excluding any relevant literature.
		The search strategies are logical.	Thank you.

Commentator & Affiliation	Section	Comment	Response
		It would be helpful for the reader to have here in a table or appendix the definitions of the outcomes criteria-some are obvious, some are not. For example a brief description of each scale chosen, and some reasoning why these scales were chosen (commonly used in literature, and if there are meaningful clinical differences (MCIDs) for what level of improvement in scales. Also, include briefly what the scores mean for each scale.	Thank you for this comment. Within the glossary we define the outcomes, provide the standard scale sued to measure the outcome, what the results mean, and any information for meaningful differences that apply.
	Results	Page 12-13 'Study characteristics' seems like a lot of detail before the key points and the detailed analyses. Consider reporting key descriptors of the studies. For example, do you need to report both weight and bmi for the general study	Thank you for this comment. We have attempted to be complete and comprehensive in giving the reader details about the included studies. The example which you provide is reported that way since some studies report weight using the BMI and other kg. Therefore, to be more complete, we have chosen to report data in such a way.
		Page 12. Under 'Study Characteristics' Only one study was poor quality and excluded, what was the response for the poor rating?	Thank you for this comment. We do not make any exclusions based on study quality. All included studies are rated for quality which impacts the strength of evidence.
		P13 under 'studies comparing systematic bio agents with photo therapy. Line 20, one observational of study…would be helpful to put the 'n' here.	Thank you for this comment, we have added the data you have requested.
	General	For an overview, Consider listing out potential comparisons with the n of studies found for each comparison.	Thank you for this comment. The specific comparisons in each study as well as the sample size can be found in Appendix Table 4.
		Key Question1 Key points-Most statements list the grading of evidence, but not all. Was the mixed treatment comparison graded?	No, the MTC was not included in grading strength of evidence. We have clarified this in the methods section under grading the strength of evidence by explicitly stating indirect comparisons were not included in the grading.
		Detailed Analysis For the studies described in detail, its helpful to the reader if the study type, N, population, study length and dosing of drugs is noted. Otherwise, it's hard for the reader to judge the study.	Thank you for this comment. The study type, specific comparisons in each study, sample size, inclusion and exclusion criteria, study length, and drug dosing can be found in Appendix Table 4.
		Since most of the studies are good or fair, consider calling out (stating) only the levele of evidence for the good or the poor studies.	Thank you for this suggestion. To minimize the need for the reader to refer to an appendix table, we have included the study quality for each study throughout the text.

Commentator & Affiliation	Section	Comment	Response
		Page 18, line 41, 'authors concluded'. Would rather not have what the authors of a study concluded, but rather what the authors of this comparative review conclude based on their evaluation of the study.	Thank you for this comment. When presenting the results of studies, often times investigators were vague in reporting specific numerical data and therefore we were left with concluding statements made within the manuscript. We have taken the time to synthesize the results in our discussion chapter.
		Page 19, line 43, if the authors want to take into account the results of a poor study, its best to justify why.	Thank you for this comment. No studies were excluded based on their individual quality. However, the quality of studies for a particular comparison and outcome was taken into account when grading the strength of evidence, as risk of bias was one of the four domains used.
		Indirect comparisons page 22-would be helpful to have some detail about what this population looked like.	Thank you for this comment. We have added more details regarding the patient population studied in this analysis based on what was reported in their manuscript.
		Page 23, class level comparisons- line 20-were the patients naïve to methotrexate as well?	Thank you for this comment. Reporting of whether a patient was naïve to therapy was somewhat incomplete and inconsistent across trials. We reported all information regarding this data point that a study provided.
		Key Question 2 and 3 Same general issues to help improve clarity as noted in KQ1	Noted, thank you.
	Discussion/ Conclusion	Good summary of the relative lack of comparative evidence. Unfortunate to see the short time frames of the available studies for efficacy and harms. Applicability section is good. Research gaps are well stated.	Thank you.
	Clarity and Usability	f. Clarity and Usability: Well structured and succinct. However the key points can get lost in the acronyms. Suggest providing info on whether the improvements certain scores are meaningful clinically. This is mentioned in the discussion for one study, but what about others.	Thank you for this comment. We use the discussion section to point out statistically significant findings of higher levels of strength of evidence. With that, we also provide information about clinically meaningful differences.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer 7	General	1. Several intra-individual half-side comparison studies have addressed the efficacy of narrow-band UV irradiation in biologic (alefacept, adalimumab, etanercept or ustekinumab)-treated patients. However only on of those studies (Legat et al) was identified and then excluded from the analysis. Were the other studies overlooked? Moreover, from the inclusion and exclusion criteria it is not clear why such studies (would) have to be excluded from the analysis. This needs to be clarified.	Thank you for this comment. Included studies had to either: 1) compare a biologic versus a nonbiologic or phototherapy, or 2) describe a population being transitioned from a biologic to a nonbiologic or phototherapy. Studies which evaluated combination therapy were excluded and were not a focus of this report.
	Results	2. In Results significant weight gain is reported for the treatment with certain biologics. However, this is not (adequately) addressed in the discussion.	Thank you for this comment. Although there was a significant increase in weight from baseline in the etanercept group, the change in weight in the etanercept group was not compared to the change in weight in the methotrexate group in this study. Therefore, it is unknown whether the observed changes are statistically significant or not between etanercept and methotrexate. We have clarified in the results section the between group comparisons were not made in the study.
		3. Page 15, line 14; study by Inzinger et al: "although did not make statistical comparison between the groups". This statement is not correct. The authors made clear statistical comparisons between the different treatment groups and provided p-values, indicating the superiority of oral PUVA (8-MOP and 5-MOP+UVA pooled together) vs. certain biologics. However, in the present health care report only the data for 8-MOP plus UVA are presented since 5-MOP is not approved in the US. P-values for comparing 8-MOP plus UVA vs. each of the biologics could be easily calculated by using exact Wilcoxon test and included in the health care report.	Thank you for raising your concern. The Effective Health Care Program is intended to provide information to inform practice. As such, research focuses primarily on medications and interventions that are currently available to patients and practicing clinicians. Therefore, the statistical comparison presented in the paper which includes a non-FDA approved agent (5-MOP) could not be used. We presented all data in the form which it was reported for all studies and did not calculate any statistics separately.
		4. Page 46 and 47: The general wording concerning the study of Inzinger et al for the comparison of PUVA vs. each of the different biologics is repetitive. The wording could be condensed. Moreover, the same issue as addressed above for Page 15 applies to page 46 and 47.	Thank you for this comment. Given the size of the report and multiple authors, we have made attempts to standardize the presentation of data so that the report flows more cohesively and clearly.

Commentator & Affiliation	Section	Comment	Response
		5. The reasons for excluding specific reports should be included in Table 1 and 2 of the Appendix, based on the listing in Figure 2 (page 31). This could be easily done by e.g. adding a certain letter/number to the list for a specific exclusion criterion.	Thank you for this comment. The reason for exclusion, which corresponds to the reasons in Figure 1, is listed in Table 1 and 2 of the appendix. The first row of each section of excluded studies provide the reason why that section of studies was excluded.
		6. Whenever the authors report on transition studies (several times throughout the manuscript), the order of wording for the different treatments seems to be odd. For instance, on page 38, line 11: "transition between the biologic agent adalimumab and the non-biologic agent methotrexate". In fact, the transition was from methotrexate to adalimumab; in other words methotrexate was given first and adalimumab second. The same order should be used in the text of the report.	Thank you. We have made the change.
		7. Table 7: It is not entirely clear for which time point the PASI values are listed. PASI should be given for all time points, i.e. baseline, week 12 and week 24. Moreover, it is not clear which groups were compared to each other.	Thank you for this comment. We have provided the PASI for both 12 and 24 weeks. The three columns at the end of the table listing the p-values are titled according to the comparison which the p-value describes. The description of comparisons is provided in the text above the table.
		8. All tables should contain the reference numbers or first authors/year of the different studies listed (e.g. lacking in Table 8).	Thank you for this comment; we have added citations into table 8.
Amgen **Joshua J. Ofman, MD, MSHS**	General	Thank you for the opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ) draft report entitled: "Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis" (herein referred to as "Draft Report").[1] Amgen Inc. (Amgen), a science-based, patient-driven company that is committed to using evidence-based science and innovation to dramatically improve patients' lives, manufactures etanercept (trade name Enbrel®).[2] Etanercept is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Amgen has conducted many clinical trials in the inflammation therapeutic area to demonstrate the safety, efficacy, and effectiveness of etanercept.[3] As such, Amgen's clinical experts have a deep understanding of the challenges of conducting clinical research in this field and the limitations in the literature surrounding the comparative effectiveness of biologic agents. Amgen commends the authors for a well-written Draft Report. Following a careful, scientific review of the Draft Report, Amgen offers the following specific comments and urges the authors to consider and address them before issuing a Final Report:	We would like to thank the reviewer for the comments.

Commentator & Affiliation	Section	Comment	Response
	Introduction	The background section on page 2 states that, "Currently, three biologic TNF-alpha inhibitors (infliximab, etanercept, and adalimumab), one T cell-targeting agent (alefacept), and one anti-IL 12/23 agent (ustekinumab) have approval from the U.S. Food and Drug Administration (FDA) for psoriasis treatment." Enbrel is indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.[4]	Thank you for this comment. We incorporated three tables into the introduction to provide details for all agents that are evaluated in this comparative effectiveness review.
	Executive Summary	In the executive summary, page ES-12 it states that, "For the comparison of adalimumab versus methotrexate, infliximab versus methotrexate, and etanercept versus acitretin, there is low strength of evidence favoring the individual biologic agent versus the nonbiologic agent". In Table ES-1 it shows that the strength of evidence comparing etanercept to acitretin is moderate.	Thank you for this comment. We use the *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews* in determining the strength of the body of evidence and the methodology is specified in the report. Strength of evidence is related to the confidence that we have that future well conducted studies/trials will not likely change the conclusions. In Table ES-1, there is a moderate strength of evidence favoring etanercept versus acitretin for one intermediate outcome --- PASI. We have altered the statement somewhat based on reviewer's comments on page ES-12. "For the comparison of adalimumab versus methotrexate, infliximab versus methotrexate, and etanercept versus acitretin, there is *predominantly* low strength of evidence favoring the individual biologic agent versus the nonbiologic agent."
		On page 31 of the report it states that five patients in a trial by Barker et al experienced infusion-related reactions in the infliximab group whereas in Appendix F Table 11, it states that 17/649 patients experienced an infusion related reaction.	Thank you for this comment. Five patients who experienced an infusion-related reaction on page 32 are from 63 patients who transitioned from infliximab group to methotrexate. Seventeen patients who experienced an infusion related reaction are from 649 patients receiving infliximab. No change is needed.

Commentator & Affiliation	Section	Comment	Response
		Appendix F Table 11 indicates 1 malignancy in the infliximab group (n=649), whereas the report on clinicaltrials.gov shows 2 malignancies (1 focal nodular hyperplasis + 1 testicular neoplasm).	Thank you for your comment. Although clinicaltrials.gov results indicate 2 neoplasms (1 focal nodular hyperplasis + 1 testicular neoplasm), the manuscript by Barker et al., (Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br J Dermatol*. 2011;165(5):1109-17. PMID: 21910713.) classifies 1 basal cell carcinoma under malignancy in table 4.
		Appendix F Table 11 indicates 10 infections in the infliximab group (n=649) and 4 in the methotrexate group (n=211), whereas the report on clinicaltrials.gov shows there were 6 serious infections in the infliximab group (n=649) and 1 in the methotrexate group (n=211).	Thank you for your comment. Whenever discrepancy is noted between the manuscript and the clinicaltrial.gov results, the data from manuscript was taken. Please see the above comment for details.

Commentator & Affiliation	Section	Comment	Response
		On page 31 of the report, it states: "…Adverse events for this population were reported in the results posted on www.clinicaltrials.gov for the period of time after the therapy switch (weeks 16 to 26). No patients experienced hepatic enzyme elevation or TCP after the switch. One patient was reported to have hypertension in *the methotrexate group* (1.59 percent) while no cases occurred in the infliximab group (p=NR). *Five patients (8 percent)* experienced infusion-related reactions in *the infliximab group*. A variety of infections were reported including bacterial arthritis, febrile infection, Lyme disease, streptococcal pharyngitis, pneumonia, pulmonary tuberculosis, staphylococcal infection, and viral infection. Of all of these infections, one case of bacterial arthritis (1.59 percent) and one case of staphylococcal infection (1 percent) occurred in *the methotrexate group* while no events occurred in *the infliximab group* (p=NR)." Based on report on clinicaltrials.gov, it should read [changes are italicized]: "…Adverse events for this population were reported in the results posted on www.clinicaltrials.gov for the period of time after the therapy switch (weeks 16 to 26). No patients experienced hepatic enzyme elevation or TCP after the switch. One patient was reported to have hypertension in *patients who switched from methotrexate to infliximab* (1.59 percent) while no cases occurred in the infliximab group (p=NR). *Eight* patients experienced infusion-related reactions in *patients who switched from methotrexate to infliximab*. A variety of infections were reported including bacterial arthritis, febrile infection, Lyme disease, streptococcal pharyngitis, pneumonia, pulmonary tuberculosis, staphylococcal infection, and viral infection. Of all of these infections, one case of bacterial arthritis (1.59 percent) and one case of staphylococcal infection (1 percent) occurred in *patients who switched from methotrexate to infliximab* while no events occurred in *patients who switched from infliximab to methotrexate* (p=NR)."	Thank you for your comment. We incorporated the following details "One patient (1.59 percent) was reported to have hypertension in *63 patients who transitioned from methotrexate to infliximab* while no cases occurred in *9 patients who transitioned from infliximab to methotrexate* (p=NR).[36] Five patients (8 percent) experienced infusion-related reactions in *63 patients who transitioned from methotrexate to infliximab*. A variety of infections were reported including bacterial arthritis, febrile infection, Lyme disease, streptococcal pharyngitis, pneumonia, pulmonary tuberculosis, staphylococcal infection, and viral infection. Of all of these infections, one case of bacterial arthritis (1.59 percent) and one case of staphylococcal infection (1 percent) occurred in *63 patients who transitioned from methotrexate to infliximab* while no events occurred in *9 patients who transitioned from infliximab to methotrexate* (p=NR).[36]" on page 31.
		The footnote to Appendix D Table 3 for Inziger et al reads: "adalimumab, alefacept, etanercept, infliximab, ustekinumab" but the original study included efalizumab. The N of 130 reported in the table includes efalizumab.	Thank you for this comment. Because we do not include data on drugs which are not currently FDA approved, we omitted the data specific to efalizumab, which is the discrepancy you have pointed out.
		Again, Amgen thanks the authors for the overall high quality of the Draft Report and for considering Amgen's comments and suggested edits to ensure that the Final Report contains the most accurate and useful information to patients, clinicians, and other healthcare providers.	Thank you for these comments. We worked hard to generate a report that met these facets.

Commentator & Affiliation	Section	Comment	Response
		For your reference, please note that the most current Enbrel® prescribing information (last issued date: 12/2011) can be accessed at: http://pi.amgen.com/united_states/enbrel/derm/enbrel_pi.pdf. Please contact my colleague, Sarah Wells Kocsis, by phone at 202-585-9713 or by email (wellss@amgen.com) if you have any questions about this comment submission, or wish to discuss it in greater detail.	Noted, thank you.
Novartis **Amy Rudolph**	General	Please include the dose of methotrexate	Thank you for this comment. The specific dose regimens along with many other study specific details can be found in Appendix Table 4.
		Consider including discussion of risk of skin cancer with phototherapy to ensure balanced perspective	Thank you for this comment. We have mentioned the fact that longer term followup is needed to accurately capture most adverse events, including malignancy, in the discussion section.
		Please include a description of the methodology for the CHAMPION trial	Thank you for this comment. The specific details of each study included in this report can be found in Appendix Table 4.
	Executive Summary	ES-1: Unfortunately, some patients have disease that is resistant to the abovementioned therapies or becomes refractory to treatment. As a result, patients often report high levels of dissatisfaction with such approaches to psoriasis treatment.4,5,8 As written, there is an implication that patients cycle thru multiple therapies, but this is not entirely accurate as many patients are not even exposed to biologics. Thus, the SOC may need to be improved.	Thank you for this comment. We have revised our terminology as this was not our intention.
		Pg. 13: The percentage of participants with concomitant psoriatic arthritis ranged from 25.0 to 41.5 percent. Please include how psoriatic arthritis was diagnosed	Thank you for your comment. We have added the details you requested.
		Pg 26: A lower proportion of ustekinumab treatment courses resulted in complete remission (6 percent versus 21 percent, p=NR), PASI90 (39 percent versus 70 percent, p=NR), PASI75 (67 percent versus 89 percent, p=NR), and PASI50 (89 percent versus 92 percent, p=NR) compared with PUVA therapy. Please state how long remission was maintained	Thank you for this comment. The duration of remission was not reported in the manuscript. (Inzinger M, Heschl B, Weger W, et al. Efficacy of psoralen plus ultraviolet A therapy vs. biologics in moderate to severe chronic plaque psoriasis: retrospective data analysis of a patient registry. *Br J Dermatol*. 2011;165(3):640-5. PMID: 21564068.) We added this detail as requested.