

Comments to Research Review

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Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes

Citation: Qayyum R, Wilson LM, Bolen S, Maruthur N, Marinopoulos SS, Feldman L, Ranasinghe P, Amer M, Bass EB. Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults With Type 2 Diabetes. Comparative Effectiveness Review No. 14. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-02-0018.) Rockville, MD: Agency for Healthcare Research and Quality. September 2008. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comment, by Section	Response
Executive Summary	
<p>Comment: A statement under Gaps in Evidence and Future Directions for Research (page ES-4) states, Probably the most important comparative study that needs to be performed should compare premixed insulin analogues and a combination of bolus insulin injections with rapid-acting insulin analogues plus a basal insulin injection with long-acting insulin analogues?. <i>[Identifying information redacted]</i> agrees and have completed a Phase III randomized controlled clinical trial (<i>[Identifying information redacted]</i>). The results were published in 2008. The citation is: <i>[Identifying information redacted]</i></p>	<p>Thank you very much for this suggestion. We captured this article when we conducted an update of our literature search.</p>
<p>Under Conclusion (pages ES-3 through ES-7), several inconsistent conclusions were observed between text and table. For example, when weight gain was compared between premixed insulin analogues and long-acting insulin analogues, text on page ES-3 states, Premixed insulin analogues appear to have? an increased risk of weight gain although evidence is not very strong but no results are reported in Table A (page ES-7).</p>	<p>We have corrected this inconsistency.</p>
<p>Executive Summary doesn't include any Applicability findings.</p>	<p>We have included a section on applicability.</p>
<p>Need reference(s) (page ES-1): Premixed insulin preparations are appropriate for patients who? (6) have a hemoglobin A1c (HgbA1c) greater than 8.5% despite maximal therapy with oral antidiabetic agents.</p>	<p>Thank you very much for your comment. We generally do not put references in the executive summary.</p>
<p>Recommend changing "effectiveness" to "efficacy" since no observational studies were included in the systematic review.</p>	<p>In the updated search, we found one effectiveness study that fulfilled our inclusion criteria and is included in the systematic review. However, we argue that studying "effectiveness" does</p>

	not mean the same thing as including observational studies in a systematic review. According to the Draft Guide for Comparative effectiveness reviews, posted on the Effective Health Care website, "comparative effectiveness review examines the efficacy data thoroughly to ensure that decision makers can assess the scope, quality, and relevance of the available data and points out areas of clinical uncertainty."
Rate of hypoglycemia was reported by different types of hypoglycemia (e.g., serious, daytime, nighttime) in the Evidence Table but not under Executive Summary.	Thank you for your suggestion. We have specified types of hypoglycemia in the executive summary.
<i>[Identifying information redacted]</i> is pleased to submit comments on the Draft Report on Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes (the Report) released by the Agency for Healthcare Research and Quality (AHRQ) on February 29, 2008. <i>[Identifying information redacted]</i> is a biopharmaceutical company dedicated to improving patient lives through discovery, development and commercialization of innovative medicines. <i>[Identifying information redacted]</i> appreciates the opportunity to comment on this draft report related to comparative research on diabetes medicines and looks forward to working with AHRQ to implement appropriate methods for comparative studies, particularly as it relates to diabetes.	Thank you for your comments.
<i>[Identifying information redacted]</i> supports comparative studies in healthcare to the extent they benefit patients and uphold the ability for a physician to make clinical decisions in the best interest of the patient. More broadly, we appreciate AHRQ's earlier development of the Guide for Conducting Comparative Effectiveness Reviews (the Guide) released October 10, 2007. AHRQ has taken steps to ensure stakeholder involvement in the Effective Health Care Program studies; however, we feel strongly that transparency is paramount and that stakeholders should be involved early on and throughout the process. <i>[Identifying information redacted]</i> urges the Agency to make public its research questions, rationale for selecting those questions and how and to whom reports will be communicated	Thank you for your comments. AHRQ is responsible for the development of the topic and key questions. Additional descriptions of the topic and key question development processes will be added to the website.
We would first like to thank the AHRQ for the opportunity to comment on the draft report entitled Comparative Effectiveness, Safety, and Indications of Insulin Analogues in Premixed Formulations for Adults with Type 2 Diabetes.	Thank you for your comments.
Our three main areas of comment are as follows: 1. Differences among the specific study populations utilized in the randomized controlled trials included in this comparative effectiveness review may limit the generalizability of the findings as well as the ability to draw inferences regarding the effectiveness of premixed insulin analogues.	Thank you. We have included this point under the applicability heading.
2. The overall, apparent improvement in glycemic control (HbA1c) with premixed insulin analogues relative to long-acting insulins (eg, insulin glargine) may be explained by the higher daily dosage of the premixed analogue utilized in the selected studies included in the review. In addition, this apparent improvement in glycemic control with premixed insulin analogues	We have pointed this out in the results section of the report.

<p>relative to long-acting insulins potentially comes at the expense of added patient risk in terms of more hypoglycemic events and weight gain.</p>	
<p>3. We applaud this comprehensive effort as well as the due diligence undertaken to identify gaps in the evidence, particularly the need for studies comparing premixed analogue insulins with regimens consisting of a long-acting insulin as basal insulin plus a rapid-acting insulin as bolus insulin. We would also like to take this opportunity to bring to the attention of AHRQ a number of ongoing studies comparing premixed insulin analogs to combination regimens of long- and rapid-acting insulins that could potentially address some of the evidence gaps identified in this report.</p>	<p>Thank you for your comments.</p>
<p>The remainder of our comments to this draft report relate specifically to the facts reported from selected studies comparing premixed insulin analogues to long-acting insulins. Specifically, we will share a number of inconsistencies identified in the data cited and will bring attention to the lack of dose equivalence between premixed insulin analogues and long-acting insulins in these studies.</p>	<p>Thank you for your comments.</p>
<p>This comparative effectiveness analysis and corresponding draft report focus on a comparison of pre-mixed insulin analogue products with other insulin products alone or in combination as opposed to comparisons of specific insulin regimens. We would suggest that the AHRQ consider clarifying that the orientation of the analysis was related specifically to product comparisons and cite that there may be limitations interpreting the report as it relates to physician best practices, standards of care, or expert consensus guidelines, all of which could diminish the clinical relevance and utility of the report.</p>	<p>We have mentioned this in the discussion section.</p>
<p>In addition, it is suggested that the report needs to convey that treatment decisions about insulin regimens need to be individualized since patients with diabetes mellitus present with a wide spectrum of blood glucose profiles. Common patterns of blood glucose profiles in patients with type 2 diabetes include fasting hyperglycemia, postprandial hyperglycemia, or both fasting and postprandial hyperglycemia (Mooradian et al, 2006). These profiles represent a deficiency in basal or post-prandial insulin secretory capacity or both, and are differentially addressed by long-acting insulins, a combination of long- and rapid-acting insulins, or premixed insulin preparations. This reinforces the need to insure that the head-to-head comparisons of insulin preparations are interpreted relative to the study population identified for inclusion in the study. For example, among the 10 studies selected for the comparison of premixed insulin analogues to long-acting insulins, in seven of the studies (Holman 2007, Tamemoto 2007, Jacober 2006, Kann 2006, Kazda 2006, Raskin 2005, Malone 2004), the study subjects were insulin naïve prior to randomization whereas in three of the studies (Cox 2007, Roach 2006, Malone 2005), the study subjects were failing basal insulin therapy prior to randomization. There are also differences among these studies with respect to insulin titration targets (eg, fasting blood glucose targets < 120 mg/dL versus < 100 or 110 mg/dL). Other relevant differences between study populations might include age, level of glycemic control, and duration of diabetes. The failure to take into account such differences in the</p>	<p>We have mentioned this in the discussion section.</p>

<p>specific study populations evaluated may again limit the interpretation and generalizability of the findings.</p>	
<p>Finally, the comparison of premixed insulin analogues versus a combination of long- and rapid-acting insulin analogues (p. ES-3) is based on a single non-randomized trial (Joshi 2005). We suggest adding the study by Rosenstock et al (Rosenstock et al, 2008a), which compared prandial premixed therapy with basal/bolus therapy in type 2 diabetic patients. This study demonstrated that patients in the basal/bolus therapy group achieved a statistically significant greater HbA1c reduction than patients in the premixed therapy group. Furthermore, a statistically significant greater percentage of patients achieved an HbA1c < 7.0% and < 6.5% in the basal/bolus therapy group compared to the premixed therapy group with similar rates of hypoglycemia for both treatment groups.</p>	<p>Thank you very much for this suggestion. We captured this article when we conducted an update of our literature search.</p>
<p>References: Mooradian AG, Bernbaum M, Albert SG. Narrative Review: A Rational Approach to Starting Insulin Therapy. <i>Ann Intern Med.</i> 2006; 145:125-134. Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal/bolus (glargine/lispro) therapy. <i>Diabetes Care.</i> 2008; 31:20-25.</p>	<p>Thank you for your suggestions.</p>
<p>Consider revising the executive summary in the light of the comments made above. Additional minor comments include: Page ES -1: Fourth paragraph: "This alteration alters...." consider rewording the sentence as "this alteration changes....". Also pharmacokinetics of insulin, and not the "insulin analogue". Also "premixed insulin analogues may provide more physiologic glucose lowering profile..." More physiologic compared to what? If it's compared to a single injection of insulin the answer is yes, but when compared to basal-bolus regimen it is not. Similarly, "more flexibility in timing their meals" more compared to what? Compared to premixed human insulin preparations.</p>	<p>Thank you. We have made appropriate changes as suggested.</p>
<p>Could you please clarify the following seeming inconsistency with the following two statements: 1) Table A, pg. ES-5 of the CER, under 1a: Premixed insulin analogues are not similar to premixed human insulin preparations in lowering fasting glucose. 2) Pg. 20 of CER: Key Messages section, Fasting Glucose, second bullet: Premixed insulin analogues are similar to premixed human insulin preparations in lowering fasting glucose.</p>	<p>We have clarified this sentence.</p>
<p>Questions concerning the following Key Messages taken from Table A, Page ES-6: • Premixed insulin analogues may be better than oral antidiabetic agents in lowering postprandial glucose although the evidence is not strong. LOE Moderate • There is insufficient evidence to determine whether premixed insulin analogues are better</p>	<p>We have clarified this statement and separated exenatide in the key messages.</p>

<p>or worse than exenatide (incretin mimetic agent) in lowering postprandial glucose. LOE Moderate Can the first bullet be clarified? The Eisenberg Center generally uses an Insufficient Evidence statement such as: There is insufficient evidence to determine if premixed insulin analogues are better or worse than oral antidiabetic agents in lowering postprandial glucose. Could you please clarify the evidence ratings for both these bullets?</p>	
<p>In Table A, page ES-5 of the CER, the third section under 1b. Postprandial Glucose (see bullet below): For the key message below, the CER uses LOE of “No Evidence”, is this equivalent to “Low”? • There is insufficient evidence to compare premixed insulin analogues with a combination of long-acting and rapid-acting insulin analogues in lowering postprandial blood glucose. LOE No Evidence (Should this be Low?)</p>	<p>We have corrected this - it is "low".</p>
<p>In Table A, page ES-6 of the CER, section 1c, fourth key message in CER is: • Premixed insulin analogues are as effective as NPH/regular 70/30 in lowering HgA1c. LOE High Because NPH/regular 50/50 is used in 1 trial, would it be more accurate to say the following: Premixed insulin analogues are as effective as premixed human insulin in lowering HgA1c. LOE High</p>	<p>Yes, it is accurate.</p>
<p>Please clarify your conclusions summarized in Table A and throughout the report: When the authors mention "glucose", such as "fasting glucose" or "postprandial glucose", are the authors referring to <u>whole blood</u> or <u>plasma</u> glucose measurements?</p>	<p>We have clarified this in the methods section, and made appropriate changes in rest of the report.</p>
<p>unclear what 'their' refers to - it is the patients cited in the last sentence of the preceding paragraph. Rephrase so that the word 'their' is clear.</p>	<p>We have clarified this sentence.</p>
<p>Specific edits within the documents</p>	<p>We have accepted most of the edits except those noted below.</p>
<p>in a study of evidence-based medicine, this statement is unsupported by evidence. The addition of insulin can result in <i>improved FLEXIBILITY of meals and activities</i>, at least relative to some other medications (e.g. sulfonylureas). So this blanket statement is not justified. Also, this statement only applies to cedrtain forms of insulin therapy, e.g. premixed insulins (if there is data to support that) and it does not apply to MDI (multiple daily injections) nor to the long acting insulin analogues given alone. SO it would be incorrect to make a blanked statement that insulin therapy reduces flexibility. That might inadvertently lead some physicians to use insulin less often, when it is likely that physicians should be using insulin more often.</p>	<p>We agree with the reviewer that not all insulin-based treatment regimens result in decreased flexibility and have reworded this sentence. We have also added a reference to the statement.</p>
<p>this is speculation that was one of the reasons for doing this study, perhaps. however, it is not a conclusion from this study. that needs to be clearly differentited and distinguished. this statement is a generalization that is not evidence based and it is likely to be incorrect. There is no evidence that use of MDI resultgs in "overall patient satisfaction wothj their treatment</p>	<p>We have re-worded this sentence so that it now clearly reads as a hypothesis and not a conclusive statement.</p>

<p>regimens". Patients may be very satisfied by virtue of the fact that they achieve better glycemic control and less hypoglycemia as compared with other treatment regimens. The section in this report dealing with quality of life was essentially inconclusive. So why include unfounded speculation here.? Also, as written, it is confusing: are the authors trying to say "multiple injections of rapid acting analogs," or "multiple injections of long acting insulin" or "the combination of multiple injections of rapid acting insulin analogues and multiple injections of long acting insulin". Note that in the "classical" or typical MDI regimen there are three injections of rapid acting insulin and one injection of long acting insulin. In some minority of cases (but perhaps up to 50%) there is a need to split the long acting insulin into two injections per day at roughly 12 hour intervals.</p>	
<p>it would be inappropriate for a report such as this to state what is appropriate or not appropriate for a given patient. this sentence could be misinterpreted. Remember that some of your readers will be hanging on every word. What you can say is that: it is common usage, or that "physicians often consider the following types of patients to be good candidates for XYZ. That would indicate that this is based on our (informal, undocumented) survey of common usage or beliefs among physicians and other health care providers, and it is not a conclusion of the present study per se.</p>	<p>We have reworded this sentence to reflect that this is a mere suggestion and not an endorsement.</p>
<p>what is meant by consistent meals? not exactly the same thing. I think we want to say that the meals have approximately the same composition in terms of calories, carbohydrates, simple carbohydrates, complex carbohydrates, fiber and fat -- i.e. factors that affect glycemic index, and rate of gastric emptying. (it is not just amount of carbohydrate). But we need a better definition of what is meant by consistent, perhaps in a footnote. In practice that may mean that a patient is eating "more or less the same thing" and there is a great deal of latitude.</p>	<p>We have included a definition of consistent meals with parenthesis.</p>
<p>just use A1c throughout. No advantage of using A1c. The standard colloquial term had been HbA1c, but both the ADA and AACE have switched to A1c because it is simpler and easier for the patients and public to understand. There is no loss of clarity.</p>	<p>We have changed to A1c throughout our report.</p>
<p>strictly speaking this is not true. Compare the formulations of Humalog Mix and Novolog mix. In one case they mix LisPro with LPH; in the other case they mix aspart with protamine. The statement as given in the text applies to Humalog Mix but not to Novolog Mix. Although a very fine point, a document like this should get it exact. I am going by memory, so this point should be checked very carefully</p>	<p>Thank you for pointing this out. We have clarified this sentence.</p>
<p>this statement can be misinterpreted as suggesting that premixed with analogs is not appropriate for Rx of patients. What you are trying to do is to identify the raison d'etre, the reason for conducting the present study. However, it is not clear that the majority of physicians practicing in the US were "unclear the role of premixed insulin analogs. This is now one of the best established and popular methods of treatment. It may have been unclear to AHRQ, or to regulators, or to experts in evidence based medicine. But it was not unclear to the public. You need to be very careful with statements of this kind for fear that they may be</p>	<p>We have clarified this sentence.</p>

<p>misinterpreted. The authors need to indicate just what aspect of this kind of therapy is unclear, or presumably unclear, AND TO WHOM!</p>	
<p>unclear - more than what? premixed with human regular insulin? or long acting? or MDI? it is unclear what the intended comparator is.</p>	<p>We have reworded this sentence to make the comparison clear.</p>
<p>it would be good to use the term "human regular insulin" since most people use the term "regular" insulin to refer to this preparation. The subtlety that the analogues are not (exactly) human insulin may be lost on some people, including the press. This is something to address throughout the entire report to be sure that the reader clearly understands that this is "Regular or "R" insulin.</p>	<p>There were no studies in this report that compared "regular human insulin" alone with a premixed insulin analogue and therefore this confusion should not arise. We have chosen not to call premixed human insulin as "regular human insulin" due to the use of this term for another type of insulin.</p>
<p>newer than what? The authors are trying to justify the present study. the present study is legitimate, but not because the premixed analog are newer. The present study is important because this is such a popular mode of therapy, and many physicians may have difficulty deciding whether to use this or long acting alone or MDI. the term "traditional" is not appropriate. What is traditional? that will vary among different readers. Some people might think that regular qid is traditional, or NPH qd or bid? Or ultralente. or PZI. It is unclear what this means. Long acting analogs are not "traditional" - they have been on the market only a relatively short time. Yet, the text as written suggests that the premixed is new and different. It is newer than "split mixed" using regular insulin and NPH.</p>	<p>We have re-worded this sentence and removed 'newer' from the sentence and used 'alternative' instead of traditional to group other regimens.</p>
<p>does this mean alternative insulin, oral agents, oral + insulin, exenatide, or what. It is a bit vague. Does this study consider all of those?</p>	<p>We have clarified this sentence.</p>
<p>OK - is it premixed? if so there are only the two. Or, if you wish to be more inclusive there are potential mixtures of glulisine, lispro or aspart with NPH. Did you consider the latter? was it your intent to consider the latter?</p>	<p>As indicated when we present the key questions addressed in the report, we consider the three preparations as three separate premixed insulin analogues.</p>
<p>we have no evidence that there was any bias. there is the potential for bias - agreed - but the statement as written previously might imply that there was some bias - or it could be read that way. We have no evidence for or against bias. It should be sufficient to state that the study was non-randomized. period. The intelligent reader will understand the implications of that.</p>	<p>We have re-organized whole paragraph and addressed this concern.</p>
<p>given how often? bid? This comparison is very curious. this must have been a non-inferiority study and hence this guarded statement. The premixed insulins are clearly better than NPH (? bid) alone. NPH has no way whatsoever to address postprandial changes in glucose. It is non physiological. It has been replaced by both the premixed analogues and the long acting analogs or by MDI. IT WOULD BE OUTRAGEOUS to say that NPH is as good as premixed analogues or long acting analogues or MDI. NPH bid is a very poor way of given a basal insulin, and both glargine and detemir are superior to NPH. So something is seriously wrong with these studies, or with the interpretation of these studies as presented here. Some people might read this and say "OK I'll keep using NPH bid" that would be a disaster. The overwhelming weight of the evidence points to the fact that premixed (analogues or human regular), long acting, or basal bolus are superior to NPH alone. Were these patients on other</p>	<p>We have rechecked - these results are correct and these are not non-inferiority trials. We also believe that these are unexpected results and have added a sentence to convey this fact.</p>

<p>therapies for thier prandial control, e.g. sulfonylureas, glinides, alphaglucoisidase inhibitors, DPP-4 inhibitors, or exenatide. These are only two studies. How large were the studies? Were they just under-powered in terms of their ability to detect a difference?</p>	
<p>this is very surprising: the one thing that the premixed analogs do is to lower the postprandial levels - better than use of human (regular) insulin in a premixed preparationm and better than long acting analogs. However, we can expect that the premixed insulin analogues will address post-breakfast and post-dinner (evening meal) values relatively well and post-lunch values relatively poorly. It would be important in this analysis to analyze data from lunch separately from data following breakfast and dinner. (all three meals should be analyzed separately). The result present here is clearly at odds with the pharmacokinetics and pharmacodynamics. Perhaps studies were underpowered, too small, etc. What were the oral agents used? sulfonylureas? other? (metformin, TZDs ?)</p>	<p>After updating report with additional studies, the results of this comparison are much clearer and we have re-written whole paragraph to reflect revised findings.</p>
<p>are you referring to comparison of Humalog Mix and Novolog Mix, or of the comparison of a 75/25 vs 50/50 mix, or both. Specify.</p>	<p>We have clarified this.</p>
<p>were there any studies by the IHS? Did the ethnic distribution of study patients match that in the general population, or in the population in the geographic areas where the studies were performed?</p>	<p>We did not find any study even when we updated our search for this systematic review that has specifically looked at a particular subpopulation.</p>
<p>do you mean different levels of glucose control before the study (baseline characteristics) or different levels of aggressiveness for adjusting dosage in terms of algorithms and dosing, or in terms of target levels for A1c (or FPG or PPG)?</p>	<p>We have clarified this.</p>
<p>there is a serious problem with this paragraph. the first sentence sounds like you wanted to compare long acting (glargine, detemir) with rapid acting (e.g. aspart, lispro, or glulisine tid ac). One of these addresses primarily fasting; the other addresses primarily post prandial. The results will depend on whether the study population has a bigger problem with one or the other. The next sentence "jumps" to a comparison of premixed analogs with basal bolus. That is different than the comparison that is referred to in the first sentence. The writing in the second sentence is very confused and confusing. No one ever says " a combination of bolus insulin injections with rapid-acting insulin analogues plus a basal insulin injection with long-acting insulin analogues.". That is too confusing. You sholuld just say "basal bolus" and define that once, or use "MDI" referring to multiple daily injections. "</p>	<p>We have reworded this sentence to make it more clear.</p>
<p>this conclusion is not warranted ! I hav ealso commented regarding this in the Conclusions section at the end of the entire report. Yes, it would be nice to have such data. However, that dont lead to the next step, that "studies should be planned". These studies might cost 100s of millions of dollars, and might take ten years ! Thaty may or may not be the most important or wise way for the government or anyone else to spend the precious research dollars. There may be much more economical ways to do this - to get the data, e.g. small scale studies "drilling down" in various ethnic groups (e.g. through the IHS) or age groups. Population studies would need to be enormous to get patiesnt from narrow sectors, e.g. > 85 years of age, > 65 years of age, African Americans, etc etc. It can be more difficult to recruit certain</p>	<p>We did not recommend a particular study design. Such studies can be analyses of administrative data, observational studies, or other designs depending upon the resources and the need for getting a precise and accurate answer. To clarify this point, we have included "(retrospective or prospective)" in the sentence to highlight different study designs that we think can answer these questions.</p>

<p>groups, and more costly to do the studies, and more risky to do the studies (e.g. in patients with multiple complications). So simply saying that the evidence is weaker in certain areas does not justify the conclusion that more studies are needed. Such studies may be impossible to do. They may be unaffordable. A quick sketch as to the required size, duration and cost of the studies, and the difficulties recruiting, the possible liability issues, etc. may show that this "wishful thinking" is not practical or affordable, or that it is not of sufficiently high priority relative to other ways in which such funds could be spent on diabetes research.</p>	
<p>compared to what? other insulins? oral agents? oral agents + insulin? exenatide? any other antidiabetic therapies?</p>	<p>We have re-worded this sentence to make it clearer.</p>
<p>again. this conclusion is not warranted. it would be nice to have clinical outcomes studies. However, their cost may make them impossible to obtain. Perhaps what is needed is more and better post market surveillance by the FDA. Even that point is not established by the present study. Consider the size, cost and duration of such studies. Further, what we do have is A1c as a surrogate marker for the long term complications. The DCCT and UKPDS and EDIC studies have clearly shown that A1c is a pretty good surrogate marker. This use of a surrogate marker can reduce the cost and duration of studies by a factor of 100 to 1000, and possibly more. Researchers can periodically evaluate the effectiveness of A1c as a surrogate marker, but they do not have to do long term outcome studies for each therapy. If we did this for premixed insulin analogs, we would have to do it for each and every new therapy that comes along. The net result would be that NO NEW TREATMENTS WOULD EVER COME ALONG OR GET APPROVED. Do we do this for sitagliptin? for AGIs? for SUs? for glinides? for every new insulin analogue that will come along in the future. So there is a gap between the fact that we have little if any direct comparison with clinical outcomes, and the "need" to do the studies. There is a difference between "it would be nice to have" and "this is such an important question that it would be in society's best interest to evaluate this problem or question irrespective of its cost".</p>	<p>We appreciate the reviewer's concerns. However, in light of the suggestion of increased mortality in the pooled point estimates, we believe that additional clinical outcomes studies are definitely needed. We did not state that all studies need to be RCTs, as they could certainly be observational in nature as well.</p>
<p>Hello: This report doesn't state "the obvious" Long acting insulin analogs require one injection per day. In some percentage (this would be important to know) - and I'm guessing about 25 %, they require 2 injections per day. Premixed insulin users may receive 1,2, or 3 injections per day. However, the vast majority - perhaps 80 - 90% at least (again, it would be good to get data regarding this), receive the premixed insulins twice a day - before breakfast and dinner. For patients on basal insulin plus rapidly acting insulin analogs, the vast majority take 4 injections per day. Some take 5 - if the long acting insulin needs to be divided into two doses either due to the magnitude of the dose (greater than about 80 units), or because the long acting insulin fails to provide good coverage for the full twenty four hours. So, the three types of regimens have (in their most popular forms), either 1, 2 or 4 injections per day. This must impact on quality of life - not so much in terms of pain from an injection (the pain is quite small or trivial) but in terms of "inconvenience". Also, as commonly and appropriately administered, with long acting</p>	<p>We partially agree with the reviewer in principal, however, we can draw conclusions only based on the available data. We hope that soon studies will be published to illustrate the validity of the reviewer's point.</p>

insulin, most patients test SMBG once per day; those on premixed are often asked to test twice per day (to adjust each insulin dose), and those on MDI test 3 or more times per day. So, the testing - with its cost, inconvenience and actual pain, and the social embarrassment that sometimes (often) accompanies it, would be expected to result in some loss of QOL. However, if the use of MDI means that the patient gets into better control, or is thereby able to enjoy a more flexible lifestyle, then there would be an QOL.	
in what manner are they not similar? which one is better, after proper control for frequency of hypoglycemic reactions?	We have clarified this statement.
if there is no demonstrated difference, then state that there is no demonstrated difference. It would be important - indeed essential - to correct for frequency of hypoglycemia.	Due to the limited number of small studies - it is difficult to say that the two preparations are similar. We believe that we should not equate absence or lack of evidence with evidence of equivalence. In the context of meta-analysis, it is not straightforward to correct for individual patient characteristics or outcomes. We considered meta-regression, but then decided against it due to the small number of studies in each comparison.
note that some things have not been studied because IT MAKES NO SENSE TO STUDY THEM ! NPH alone is not physiological. It is not as good as regular, or rapid acting analogues for prandial coverage, and it is not as good as glargine or detemir for basal coverage. Hence it has not been studied, and it should not be studied, because its pharmacokinetics and pharmacodynamics show that it is not physiological. !	We agree with the reviewer. This is probably the reason that there were only two studies that looked at this comparison.
it would be very important to point out the interaction of insulin and TZDs in terms of weight gain and fluid retention. This effect is well established, e.g. with all of the studies of rosiglitazone and pioglitazone and this appears to be a class effect for the TZDs.	We agree with the reviewer. However, in summary tables of the executive summary we have tried summarize the evidence in the report and have avoided any discussion of the results from studies that are not part of the report.
avoid the word 'cause'. I agree that the insulin is the likely cause, but we have not established that here. Cause carries certain connotations that are avoided through the present report.	We agree with the reviewer and have avoided using "cause" wherever possible.
Introduction	
Need reference(s) (page 1): Although type 2 diabetic patients are reluctant to start insulin, insulin therapy improves quality of life in such patients.	We have added two references.
Page 4: Figure 3 is very difficult to understand. What is the meaning of the arrows leading from the subpopulations boxes to the major arrow going from comparison of outcomes? Why is there an arrow from "adherence to treatment" to the outcomes box? What is the meaning of the boxes within boxes in the outcomes layout?	We have added tables and a figure to present results concisely.
Page 5: There should be a fourth key question. I believe the last paragraph should be indented with a "4" in front.	This has been corrected.
The introduction was textbook quality	Thank you for your comments.

<p>1) On page one as well as in the Executive summary Page ES -1, third paragraph, the statement “Therapeutic alternative ... in physiologic regimen....is a premixed insulin preparations” should be reworded since premixed insulin preparation usually do not mimic normal physiology of insulin.</p>	<p>We have reworded this sentence.</p>
<p>2) Background page 1; Second paragraph: “....regimens can be either near-physiologic....”</p>	<p>We have changed physiologic with near-physiologic.</p>
<p>3) Background page 1: Check references 10-13 that show premixed insulin analogues lower postprandial hyperglycemia more than premixed human insulin to see if the timing of the injection of insulin pre-meal was set to favor the analogues. The same comments apply to the text on pages 21 and 31. When timing of the injection is adjusted such as in the study of Kilo et al ref.16, there were no differences between the premixed analogues or premixed human insulins in so far as their effect on post prandial hyperglycemia.</p>	<p>We have added a sentence to reflect timing of the insulin injections.</p>
<p>4) On page one as well as in the Executive summary Page ES -1: Of the 6 conditions that describe the potential candidate for premixed insulin preparation add another condition “those who are unwilling or not capable of mixing insulin preparations. Also the rationale for the sixth condition i.e. those with HbA1c over 8.5% is not clear but I suspect is based on a single study (Raskin et al ref 36) comparing a premixed insulin preparation with a single dose of background insulin glargine and as such cannot be construed as a reliable guideline for the general population with diabetes.</p>	<p>We have removed the sixth condition - we agree with the reviewer.</p>
<p>5) Page 5 and in the Executive Summary Page ES -2: Key question 1 item e: Rapid acting insulin analogues...with a long- <u>or intermediate</u> acting insulin analogues”. Detemir is often a twice a day preparation. The same comments apply to the body of the text.</p>	<p>Although we agree with reviewer in principal, detemir is considered 'long-acting' insulin by its manufacturer and this terminology to describe its duration of action is available in the package insert approved by FDA.</p>
<p>6) Page 5 and in the Executive Summary consider adding item f to key question 1: Effectiveness and safety of premixed insulin analogues compared to “Rapid acting insulin analogues <u>or regular human insulin</u>...with an <u>intermediate</u> acting <u>NPH human insulin</u>”.</p>	<p>Key questions were decided quite early in the process with the mutual consensus of AHRQ and EPC team and after public posting for comment. Key question 1 includes a statement that says that the comparisons are not necessarily limited to the ones listed below. This allows for the comparisons pointed out by reviewer as well as other comparisons that are not listed.</p>
<p>Methods</p>	
<p>Sensitivity analysis was conducted by taking one study out of the analysis at a time. Other sensitivity analyses for consideration include: Studies that were not analyzed using intent-to-treat principle and trials where pre-meal insulin was continued.</p>	<p>This is an excellent suggestion and we had thought about performing sensitivity analysis in several different way. However, the number of studies in each individual meta-analysis was relatively small and further stratification of trials was not possible in most, if not all, comparisons.</p>
<p>Current literature search criteria, at the Preview Level 1 (Title Review), could miss articles on QOL because QOL is not part of Key Questions. We recommend inserting "quality of life"</p>	<p>Thank you very much for bringing up this concern. We had always considered quality of life as being a part of the key</p>

<p>before adherence in Key Question #2 (page ES-2): For adults with type 2 diabetes, do premixed insulin analogues differ in regard to safety, adverse effects, quality of life, or adherence compared with other commonly used insulin preparations.</p>	<p>questions, so we feel confident that we did not exclude any articles concerning quality of life at the title review phase. We have clarified this by adding the term, "quality of life," under the Study Selection section of the Methods chapter.</p>
<p>Adherence is part of Key Question #2. However, the report does not include a separate results section on adherence except within the context of QOL (see comments 11 and 12 below):</p>	<p>We have included a separate section on adherence in the results section.</p>
<p>Treatment allocation procedure and blinding information are enclosed in the Evidence Table but not in the text under Methods.</p>	<p>In the Methods chapter under the Quality Assessment Section at the bottom of page 9 of the draft report, both blinding and treatment allocation procedure were listed as part of the quality assessment.</p>
<p>Page 11: The use of the Begg and Egger tests for publication bias is inappropriate when there is heterogeneity (see papers by Terrin et al., 2003-2005 and Lau, 2006).</p>	<p>We thank reviewer for raising this concern. Knowing the limits of Begg's and Egger's, we assessed publication bias by visual examination of the funnel plot. In the revision, we also used trim and fill method to detect publication bias.</p>
<p>It is not clearly stated what were the criteria used for deciding which treatment was effective when there were several analyses done within a category, nor what were the criteria for their being sufficient or insufficient quality for drawing a conclusion. For example, the report concludes that premixed formulations were less effective than long-acting formulations in lowering fasting glucose. However, the conclusion for the comparison of insulin aspart 70/30 is that "the difference did not reach statistical significance" (p. 27); for the other two premixed formulations there was a significant difference in favor of the long-acting formulation. How were such differences resolved?</p>	<p>The two paragraphs in the Methods section under the subheading of "Rating the Body of Evidence" summarize the methods used to grade the evidence. The methods used are described in detail in the Evidence tables appended as Table 1 in Appendix E.</p>
<p>As a non-statistician, but one who works closely with statisticians, it is my understanding that these methods are appropriate, and caveats are noted (eg inclusion of cross over studies, but not for adverse outcomes, etc). However, for dissemination purposes, it might be helpful for all of the AHRQ systematic reviews to have a reference section that explains to clinicians why this approach is appropriate and valid.</p>	<p>This is a good suggestion. AHRQ is continuing to develop a methods guide for comparative effectiveness reviews. Please refer to the Effective Health Care website for further information.</p>
<p>I am not an expert of biostatistics but as far as I can tell the statistical methods used and the metaanalytical approach is correct.</p>	<p>Thank you for your comments.</p>
<p>Very thorough and superb attention to detail.</p>	<p>Thank you for your comments.</p>
<p>Study selection page 8: Title reviews may overlook some studies. What key words were used in the title review? Insulin analogue, diabetes control?</p>	<p>A sentence clarifying this has been added to the Study Selection section in the Methods chapter.</p>
<p>On page 9 in table 2 the authors describe the inclusion criteria. In this table they describe the intermediate outcomes as: HgbA1c, fasting plasma glucose, pre-dinner plasma glucose, and postprandial plasma glucose before and after dinner.</p> <p>However, throughout the CER, the authors use terms such as "fasting glucose", "fasting blood glucose", "postprandial glucose" and "postprandial blood glucose". Please clarify the Intermediate Outcomes on page 9, should this be "blood glucose" or "plasma glucose"?</p>	<p>Edits have been made to the table.</p>

Results	
On page 79, While quality of life may directly impact adherence to a medication and thereby indirectly impact intermediate and clinical outcomes.	We have added a separate subheading for Adherence outcome.
Under Limitations (Quality of Life, page 81), The quality of life associated with choosing a particular treatment may determine adherence to therapy and should be addressed for patients with chronic diseases. However, we found very few studies that have looked at this outcome.?	We have added a separate subheading for Adherence outcome.
Executive Summary reports results on all premixed insulin analogues as a collective unit. However, in Results, the meta-analyses are conducted per specific premixed insulin analogue (lispro 75/25, lispro 50/50, aspart 70/30)	There were two main reasons why we choose to report results on all premixed insulin analogues as a collective unit. 1) the key questions were phrased with "premixed insulin analogues". 2) A separate summary of each insulin preparation would have made executive summary too long and would have defeated the purpose of a summary. While we have done so for the sake of brevity, we have pointed out significant differences between individual premixed insulin preparations in the executive summary.
Inconsistencies in the number of articles retrieved, reviewed, and included in the report. Text: retrieved 2021; included 46 articles. Graph: retrieved 3165; included 44 articles.	These numbers have now been updated to reflect the current search.
We would like to comment on the results from key questions 1 and 2 in the AHRQ draft report. Our comments are focused on providing some corrections and clarifications to the data cited from the studies comparing each of the three premixed insulin analogues to long-acting insulin that were selected for inclusion in the analysis and draft report.	Thank you for your comments.
Key Questions 1 and 2 Insulin Aspart 70/30 versus Long-acting insulin analogues 1. In the Tamemoto 2007 study, the insulin glargine dose was actually 12.0 U/day (page 27) versus 26.7 U/day for insulin aspart 70/30, and the n was 30, not 23 (page 29). Also, the description of the Raskin 2005 study (page 27) should specify the mean total insulin dose was 78.5U in the 70/30 group compared with 51.3 U in the glargine group.	Thank you for pointing out the correct number of patients in the Tamemoto et al. study. We have also added total daily insulin dose for the raskin study. We could not find other suggestions in the published reports of the articles.
2. In reference to the Raskin 2005 study (page 29), mention is made of greater reductions in A1C with insulin aspart 70/30 versus insulin glargine in patients with initial A1C greater than 8.4 (should be 8.5); it should also be noted that in patients with initial A1C less than 8.6 there was no difference between treatment arms.	We have reworded this sentence to reflect no difference in patients with A1c less than 8.6.
3. In the Holman 2007 study patients treated with insulin aspart 70/30 had lower HbA1c levels ($p < 0.001$) at study endpoint and were more likely to reach a target HbA1c 6.5% in the insulin aspart 70/30 group than in the insulin detemir group ($p = 0.001$). It is notable that the total insulin doses in this study were 48 and 42 U for the pre-mixed insulin and detemir groups, respectively (not statistically significant). This observation is relevant in the context of a recent	We are thankful to the reviewer for directing us to this study. We find it difficult to compare insulin detemir dose in a trial that compared detemir with glargine to a trial that compared detemir and premixed insulin analogue. Although study populations were similar in the two groups with respect to

<p>head-to-head comparative study of insulin detemir and insulin glargine using forced insulin titration (Rosenstock et al, 2008b), which found that similar improvements in glycemic control can be achieved with both long-acting analogues but with higher mean doses of insulin detemir compared with insulin glargine (0.52 U/kg on once daily and 1.00 U/kg on twice daily detemir compared with 0.44 U/kg glargine). Furthermore, 55% of detemir treated patients required twice daily administration. Thus, it is likely that the detemir arm in the Holman 2007 trial were insufficiently dosed. It is notable that the baseline characteristics of the study populations in the Holman 2007 and Rosenstock 2008 studies were similar with respect to glycemic control, age, duration of diabetes, weight and BMI.</p> <p>References: Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Scherthner G. A randomised, 52-week, treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. <i>Diabetologia</i>. 2008; 51(3):408-416.</p>	<p>A1c, age, duration of diabetes, and BMI, the target fasting glucose levels were different in the two studies. Holman et al. targeted a FBG of 72-99 mg/dL while Rosenstock et al (detemir vs. glargine) targeted a FBG of less than 110 mg/dl. In addition, both studies allowed insulin detemir to be administered twice daily if glycemic control was not optimal. Despite having stricter FBG criteria, only 34% of patients in the study by Holman et al needed a twice daily insulin detemir while 55% of patients in the study by Rosenstock et al needed twice daily insulin detemir. This difference in the number of patients who needed twice daily detemir may be indicative of characteristics (measured or unmeasured) which were different between the two study populations.</p>
<p>Insulin Lispro 75/25 versus Long-acting insulin analogues</p> <p>1. On page 43, the statement that insulin Lispro 75/25 more effectively lowered dinner postprandial blood glucose compared with insulin glargine in all studies except Cox 2007 is not accurate. Lispro 75/25 was more effective than glargine in lowering dinner postprandial blood glucose in the Cox study as well.</p>	<p>Thank you, we have corrected it.</p>
<p>2. On page 45, it is incorrectly stated that only the studies by Jacober 2006 and Malone 2005 reported statistically significant differences in overall rates of hypoglycemia; in the study by Malone 2004 the higher overall rate of hypoglycemia with Lispro 75/25 compared with glargine was also statistically significant (p=0.041).</p>	<p>We have rechecked it and data as stated in the report is correct. In report we stated that the hypoglycemia rate was similar in two arms in Malone 2005.</p>
<p>Insulin Lispro 50/50 versus Long-acting insulin analogues</p> <p>1. On page 54 the mean difference in fasting blood glucose between insulin glargine and insulin lispro 50/50 is reported in incorrect units: the difference is 1.7 mmol/L and not 1.7 mg/dL.</p>	<p>Thank you, we have corrected it.</p>
<p>Too many words and not enough concise use of tables and figures</p>	<p>We have added tables and a figure to present results concisely.</p>
<p>The key results outlined on pages 20-23 and also later for clinical outcomes would be much easier if put into a single figure with rows given by comparisons and columns by outcomes. A "+" or sign or filled circle might indicate the premixed form is better, a "-" sign or empty circle that it is worse, a "0" or half-filled circle by no difference and a "f" or empty cell by no data. The reader could then scan through the table and get the information quickly. As it is, the information goes over several pages and is very repetitive. You might also consider separate tables for the different preparations (see comment above on potential inconsistencies in conclusions for the different premixed formulations).</p>	<p>We have added such a figure.</p>
<p>Page 27, line 4: Should be "the remaining three studies"</p>	<p>Thank you, we have corrected it.</p>
<p>Page 38: Please provide logic behind exclusion of study by Nauck in figures</p>	<p>We have added a sentence to provide logic behind the analyses done with and without Nauck et al.</p>

Page 68-69: The conclusion that there were no statistically significant differences between premixed formulations and other medications is technically correct, however the evidence strongly favors morbidity being higher in the premixed group since the odds ratio is 2.7, could be as high as 8 and almost includes one in its 95%CI.	After updating meta-analysis with more recently identified studies, odds ratio has come down to 2.1 and 95% CI has moved to 0.87 to 5.10.
The material included comparing premixed insulin analogues to combination therapy under question 4 (first page 77) should really be included in question 1 since question 4 is addressing subgroups and this is not a subgroup analysis.	This section can be moved under Key question 1. However, we think that Key question 4 is a better place as this Key question states that "does the effectiveness or safety of new premixed insulin analogue regimens differ for individuals on oral antidiabetic agents"
Yes, The introduction and conceptual framework was nicely done. Including the Holman study and showing the results with and without it strengthens the review.	Thank you for your comments.
Comprehensive	Thank you for your comments.
1) Page 24; Hypoglycemia (also Appendix E: Evidence Table 1) The body of evidence was graded "high" for certain comparisons. I would grade that as "moderate" since the studies were not powered enough or the diabetes control achieved in the study was not optimal to augment the differential in risk of hypoglycemia	There is always some subjectivity involved in the grading of evidence and different raters may rate the same evidence differently. To decrease subjectivity and provide consistency in the grading of evidence, level of evidence grades were assigned and/or reviewed by the whole team.
2) Page 25: Describing study characteristics it would be helpful to know to what degree these studies achieved glycemic goals	each study is further individually described within its comparison group and whether that study (alone or after pooling with other studies) reached glycemic control is presented.
3) Page 27: Insulin aspart 70/30. Third and fourth line from above: One study used Detemir and the remaining four... should be remaining three used glargine	Thank you, we have corrected it.
4) Page 27: The fact that the study by Holaman et al was funded by <i>[Identifying information redacted]</i> is stated. What was the contribution of <i>[Identifying information redacted]</i> to the study of <i>[Identifying information redacted]</i> . This issue of the source of funding is covered in the section on Study Quality Assessment on page 58.	We have included all mention to the source of funding to the relevant sections and removed it from the main section of the results.
5) Page 50 and elsewhere when comparing the premixed insulin analogues to non insulin antidiabetic agents the patient population should be defined; duration of the disease or mean Hba1c etc. This information is available in the appendix Evidence Table 2 and the reader should be referred to it.	Thank you, throughout the report we have referred the reader to the evidence tables where needed.
Can evidence ratings be assigned for all Level of Evidence (LOE) statements rated as "not stated" in the Key Messages?	We would like to provide evidence ratings for all level of evidence, however, due to the large number of comparison groups and smaller number of overall studies, such an exercise will divide overall evidence in so many small segments that very little evidence will remain significant.
For any Key Message statement that also notes a comparative difference value, can the EPC please include the actual values? (Baselines and comparative values after the intervention would be most helpful.)	Actual values will be possible only for binary variables. For continuous variables - such as A1c, fasting glucose, postprandial glucose, and weight gain, it will not be possible.

For example, if the difference between fasting blood glucose between a premixed insulin analogue and its comparator is 8.9 mg/dl, please include the actual values of the fasting blood glucose in each group at the beginning of the study, and at the end of the study.	We have provided values of binary variables either in the text or in the figures in the results section.
Does the EPC agree with the following Key Message, or suggest moving exenatide to a separate message? Insulin aspart 70/30 is more effective than noninsulin antidiabetic agents, particularly exenatide, in lowering fasting glucose. The mean comparative difference between groups in 11.4 mg/dl, p=0.03. LOE not stated	No, for exenatide, there was no difference between the two groups. We have made few changes to key messages to further clarify this fact.
For the Odds ratio in the following key message, under KQ 2, section hypoglycemia: Can the authors provide the numbers used to calculate the odds ratio? Could the authors provide a confidence interval rather than a p-value? Premixed Insulin Analogues vs. Long Acting Insulin Analogues • Insulin aspart 70/30 is more likely to cause hypoglycemia compared with insulin glargine. Odds ratio 2.8, p=0.003 LOE not stated	Overall evidence for this outcome is such that a single odds ratio/confidence interval/p-value can't capture data completely. There are four different types of hypoglycemia outcomes (overall hypoglycemia, major hypoglycemia, minor hypoglycemia, and symptom-only hypoglycemia and there are three premixed insulin preparations. This will result in several odds ratios/p-values/confidence intervals.
Discussion	
Recommend adding reference(s), Current evidence suggests that in patients with higher HbA1c levels, targeting fasting glucose is more beneficial in bringing HbA1c closer to the desired target. (page 77)	We have added a reference to this statement.
Under Discussion (page 77), the following statement appears to be stronger than supported by evidence, In this systematic review we found that premixed insulin analogues were either less effective or not effective in lowering fasting glucose when compared to all other insulin preparations except rapid-acting insulin analogues. Conclusions on this topic from each section of the report are enclosed below (see comments 18-22). Two studies were included in the systematic review where 1 study found premixed insulin analogues to be more efficacious than rapid-acting insulin analogues in lowering fasting glucose but the second study found no difference.	We have reworded this statement to align it more closely with the strength of evidence.
Executive Summary (page ES-3), We found only two studies that compared premixed insulin analogues with rapid-acting insulin analogues. Both studies found a different effect of premixed insulin analogues on fasting and postprandial glucose levels.	Thank you - please see comment above.
Table A (page ES-5) Section 1a, Lack of evidence limits our ability to compare premixed insulin analogues with rapid-acting insulin analogues in lowering fasting blood glucose.	Thank you - please see comment above.
Results (page 29), Holman et al. found that insulin aspart 70/30 was more effective than rapid-acting insulin aspart in decreasing fasting blood glucose levels?	Thank you - please see comment above.
Results (page 47), We did not find any study that compared insulin lispro 75/25 to rapid-acting insulin analogues.	Thank you - please see comment above.

<p>Results (page 55), We found only one study that compared insulin lispro 50/50 with rapid-acting prandial insulin lispro? This study did not find any difference between insulin lispro 50/50 and rapid-acting insulin lispro in lowering fasting blood glucose.</p>	<p>Thank you - please see comment above.</p>
<p>We would like to comment here on each of the three sections (Key Findings, Limitations, and Gaps in Evidence) in the discussion section of the draft report. Our comments in this section focus on the lack of dose equivalence between premixed insulin analogues and long-acting insulins in the studies selected for inclusion. We would also like to take this opportunity to inform AHRQ of ongoing studies that address key gaps in the evidence base.</p>	<p>Thank you for your comments.</p>
<p>Key findings We suggest emphasis be placed on addressing the following two issues: (1) the greater total insulin doses utilized in the trials comparing pre-mixed vs. long-acting insulin therapy and (2) the tradeoff between the enhanced glycemic control with pre-mixed compared with long-acting insulin analogues and increased hypoglycemia events and weight gain.</p>	<p>We have pointed out these two issues in the Discussion section of the report.</p>
<p>The potential seriousness of hypoglycemia should figure prominently in the discussion of the clinical implications of the pre-mixed vs. long-acting insulin. Hypoglycemia is not a trivial problem from both the patient and physician perspective and in fact is a leading barrier to the effective use of insulin (Korytkowski 2002). References: Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord. 2002; 26(S3):S18-24.</p>	<p>We have reported the risk of hypoglycemia in relation to premixed vs. long acting insulin analogues in the executive summary, results section, key messages, and discussion section.</p>
<p>Limitations: We suggest addressing the potential impact of several methodological issues on the results and interpretation of comparator trials with respect to the following:</p>	<p>Please see immediately below for our responses.</p>
<p>1. Insulin dose: It is difficult to interpret treatment differences in comparator trials in which the total insulin dose as well as type of insulin vary. Specifically, the mean total dose of insulin glargine was smaller than that of the pre-mixed insulin analogue in a majority of the studies selected for this analysis (Malone 2004, Malone 2005, Raskin 2005, Jacober 2006, Kazda 2006, Robbins 2007 and Tamemoto 2007). Accordingly, we suggest noting that glargine was relatively under-dosed in comparison with pre-mixed insulin analogues in these studies. Future studies comparing equivalent total insulin doses with comparable treatment regimens in all treatment arms would provide additional insights into the true differences in effectiveness and safety among the treatments.</p>	<p>We have added this limitation in the results section while reviewing the key findings and clinical implications.</p>
<p>2. Noninferiority vs. superiority studies: Studies designed to demonstrate non-inferiority or equivalence of one treatment to another generally are not directed to optimize glycemic control and therefore interpretation of effectiveness as well as safety is challenging. For example, the rate of hypoglycemia events generally increases as lower target levels of glycemic control are reached. Thus, trials that do not try to achieve these targets minimize the treatment differences in what might otherwise be observed in either a superiority trial or in real world clinical practice.</p>	<p>We have added this limitation under the subheading of limitations in the Discussion section of the report.</p>
<p>3. Titration method: In a number of the studies (Malone 2004, Malone 2005, Jacober 2006,</p>	<p>We have pointed out this limitation of the studies in the</p>

<p>Kazda 2006, Robbins 2007 and Tamemoto 2007) the insulin dose was titrated to achieve a target fasting plasma glucose level (FPG) of <120 mg/dl instead of a more aggressive target FPG <110 or 100 mg/dl. We suggest that due to the less aggressive titration goal in these studies, the optimal dose of insulin glargine was not utilized. This may have biased the comparison in favor of the pre-mixed insulin analogue as a consequence of not facilitating the full potential of insulin glargine in controlling interprandial, nocturnal, and fasting blood glucose.</p>	<p>Discussion section.</p>
<p>Gaps in the Evidence As noted in the draft report, few studies have compared premixed insulin analogues with basal/bolus insulin therapy. In addition to the recently published study by Rosenstock et al (Rosenstock et al, 2008a) which was not included in the draft report, there are at least 3 ongoing studies sponsored by <i>[Identifying information redacted]</i> and registered with clinicaltrials.gov comparing premixed insulin analogues with the combination of a long-acting analogue as basal insulin and a rapid-acting analogue as bolus insulin. Data from these randomized controlled trials, which address this evidence gap, will be available in late 2008 and mid 2009. These studies include: <i>[Identifying information redacted]</i></p>	<p>We have updated this systematic review and have included the study by Rosenstock et al. We are thankful to the reviewer for providing this information. We have added reference to this trial in the report and will eagerly wait for the results of these trials.</p>
<p>For insulin therapy comparative studies it will be desirable to evaluate a composite outcome that includes achievement of glycemic targets while avoiding hypoglycemia, much in the same way as the study by Riddle et al (2003) did. This study compared the clinical effectiveness and associated hypoglycemia risks of insulin glargine and human NPH insulin added to oral therapy to achieve HbA1c 7% in patients with type 2 diabetes. These data could provide physicians with better insights into the effectiveness and safety of each treatment option. References: Riddle MC, Gerich J, Rosenstock J. The Treat-to-Target Trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care. 2003; 26:3080/3086.</p>	<p>We are thankful to the reviewer for pointing out the study by Riddle et al. The outcomes used in their study are quite interesting and clinically relevant. Such an outcome can be generated with individual patient data but developing such an outcome in a systematic review of studies is very likely to result in ecological fallacy. Due to the limits of the type of data that we have and a significant risk of introducing bias we did not use this composite outcome.</p>
<p>Finally, we agree with the AHRQ draft report that additional comparative studies of premixed insulin analogues versus basal/bolus insulin regimens on patient reported outcomes such as quality of life and treatment satisfaction are needed. One such study sponsored by <i>[Identifying information redacted]</i> and described above (<i>[Identifying information redacted]</i>) has recently been completed and data will be available in late 2008. We concur with the observation that comparative studies of sufficient duration with appropriate statistical power to evaluate long-term outcomes such as cardiovascular disease morbidity and mortality are needed.</p>	<p>Thank you for your comments.</p>
<p>Pagination is off. There are two page 77 and 78.</p>	<p>We have corrected this.</p>
<p>Yes. (see first comment).QOL and impact in subpopulations, especially older individuals was explicitly stated.</p>	<p>Thank you for your comments.</p>
<p>Comprehensive and well stated</p>	<p>Thank you for your comments.</p>
<p>1) Page 77, the third paragraph should be reworded to avoid the impression that twice daily premixed insulin can be physiologic or is comparable to basal-bolus regimen requiring four</p>	<p>We have added a sentence to reflect this limitation of premixed insulin preparations.</p>

<p>injections a day. In general, premixed preparations assume that a single proportion of fast and intermediate acting insulin is suitable for all patients. This is contrary to the current wisdom that insulin therapy should be highly individualized and people should refrain from adopting "one size fits all" attitude. Because of such concerns the pharmaceutical industry has made available premixed insulin preparations of various proportions of which only 70/30 and 50/50 are available in the US.</p>	
<p>2) Page 77, the paragraph on Fasting Glucose: I disagree with the statement that patients with very poor fasting blood glucose levels or very high Hba1c levels do not benefit as much from the premixed insulin regimen. Indeed the study of Raskin et al (Ref. 36) showed that the benefit of insulin aspart 70/30 compared to glargine was seen in patients who had HbA1c higher than 8.4% while those with milder fasting blood glucose or HbA1c elevation the efficacy of the two insulin preparations were comparable.</p>	<p>We are thankful to the reviewer for raising this concern and we have removed this sentence from the discussion.</p>
<p>3) Page 77, the section on post-prandial: comparing the premixed insulin analogue to premixed human insulin should be done only when the two preparations are used correctly in so far as the timing of injection in relation to meals (similar to the study of Kilo et al). All the studies comparing the premixed analog with premixed human insulin should be reviewed to verify that the injection time was correctly implemented in the study.</p>	<p>We have pointed out the differences in the timing of premixed human insulin in relation to meals in the discussion section.</p>
<p>4) Page 79, the last sentence of the first paragraph. The <i>[Identifying information redacted]</i> retrospective observational study is supposedly completed by January 2008; if the data is available it should be incorporated in the updated manuscript. A sentence about the recent revelations from the ACCORD trial as to the mortality risk of very tight blood glucose control (HbA1c of 6.4%) might be worthwhile.</p>	<p>We have referenced ACCORD trial in the Discussion section. The <i>[Identifying information redacted]</i> study has not yet been published.</p>
<p>this is a serious error: there is no clinical use of "basal insulin injections with long acting insulin analogs": basal insulin is given in the form of long acting insulin analogs so these two are redundant: we never combine "basal insulin" with "long acting"; basal insulin IS long acting and long acting is basal. Itg would be embarrassing to publish this as currently stated. Perhaps the authors meant: need to compare biphasic with MDI (long acting + rapid acting) AND need to compare biphasic with basal. However - this aspect has been covered, and covered quite well in the present review.</p>	<p>We have reworded this sentence to clarify it.</p>
<p>can look at data from long term followup of patients receiving various medications, without randomization. this will also apply to to item "7" (1) above.</p>	<p>We understand that various factors are involved in the selection of study design to answer research questions and one study design may not answer all clinically relevant questions. Therefore, we have only suggested a research question and the choice of a study design is left to the investigator.</p>
<p>again, before conducting an extensive and expensive study, it would be valuable to review data from large clinical databases, e.g. the VA, the military, the large "Kaiser-like" HMOs to</p>	<p>We agree with the reviewer that review of large clinical databases may be a cost-effective way to answer this</p>

see if there is any suggestion of effects in these various subpopulations.

question. Our intent is to point out gaps in evidence and possible directions for future research and not to suggest a particular study design to researchers.

Hello:
This report doesn't state "the obvious"
Long acting insulin analogs require one injection per day. In some percentage (this would be important to know) - and I'm guessing about 25 %, they require 2 injections per day.

Premixed insulin users may receive 1,2, or 3 injections per day. However, the vast majority - perhaps 80 - 90% at least (again, it would be good to get data regarding this), receive the premixed insulins twice a day - before breakfast and dinner.

For patients on basal insulin plus rapidly acting insulin analogs, the vast majority take 4 injections per day. Some take 5 - if the long acting insulin needs to be divided into two doses either due to the magnitude of the dose (greater than about 80 units), or because the long acting insulin fails to provide good coverage for the full twenty four hours.

So, the three types of regimens have (in their most popular forms), either 1, 2 or 4 injections per day. This must impact on quality of life - not so much in terms of pain from an injection (the pain is quite small or trivial) but in terms of "inconvenience". Also, as commonly and appropriately administered, with long acting insulin, most patients test SMBG once per day; those on premixed are often asked to test twice per day (to adjust each insulin dose), and those on MDI test 3 or more times per day. So, the testing - with its cost, inconvenience and actual pain, and the social embarrassment that sometimes (often) accompanies it, would be expected to result in some loss of QOL. However, if the use of MDI means that the patient gets into better control, or is thereby able to enjoy a more flexible lifestyle, then there would be an QOL.

All the points raised by the reviewer may actually be true. Based on the findings of this systematic review of the currently available evidence, we don't think that there is enough evidence to comment on the long-term effects of different insulin-therapy regimens on quality of life.

this comment is too strong. There is no evidence of heterogeneity of results in different populations. In the absence of some evidence - even weak evidence to that effect, this may send the wrong message to insulin therapy. All you can say and what should be said instead of this sentence, is that "At present there is no evidence to suggest that these conclusions do not apply to various subgroups of the population. However, most studies have not been designed to test this, and these studies had very low statistical power to detect such effects. Before arguing that more studies need to be done with more subpopulations, longer duration, and examining clinical outcomes: the authors should consider the potential and cost of such studies. Would it be worth 100 million dollars or 200 million dollars and 109 years - to do a study like the DCCT or UKPDS to address the (subtleties) of insulin administration? Frankly probably not! Any such study would have to compete for funding and attention with multiple other kinds of clinical studies that are currently ongoing and

We disagree with the assertion that if a certain insulin preparation is shown to be effective in diabetic patients without significant comorbidities, we can conclude that it will be effective in diabetic patients with significant comorbidities. We believe that this conclusion can only be reached after certain assumptions. We have added a sentence of this effect in the conclusion subsection of the discussion section. We also disagree with the assertion that studying the effects of premixed insulin analogues on long-term clinical outcomes will be a waste of scarce resource. Rosiglitazone is a recent example where improvement in intermediate outcomes (glycemic control) did not translate into improvement in

<p>planned, or that will be planned over the next 10 - 15 years. So while there is a "gap" (a partial gap to be more exact) in our knowledge in this area - it is taking a step or leap beyond that to call for new studies - not adequately defined - to close that knowledge gap. By the time such a study was completed, the entire landscape for insulin therapy of diabetics might be radically different. The important questions at that time, is whether one should use insulin pumps, new analogs that would become available by then, combinations of insulin or pramlintide, etc. etc. So while these are interesting and legitimate questions, the present study does not lead to the conclusion that these kinds of studies should be done. What you can say, is that "the medical and scientific community should <i>consider</i> whether studies of this nature would be appropriate, feasible, cost-effective, and likely to provide societal benefit, such that they should be added to the list of research studies that should be considered for the future. THERE IS A REAL DANGER THAT THIS CONCLUSION WILL BE MISINTERPRETED BY SOME PARTIES, TO LEAD TO LONGER, LARGER AND WIDER STUDIES OF NEW PHARMACEUTICAL AGENTS, RESULTING IN A DELAY IN GETTING NEW TREATMENTS TO MARKET, AND RESULTING IN EVEN FURTHER INCREASES IN THE COSTS FOR GETTING NEW DRUGS THROUGH THE REGULATORY PROCESS. THERE IS NOTHING IN THE PRESENT REPORT THAT WOULD JUSTIFY THE NEED FOR A MORE SLOW, EXPENSIVE, AND RIGOROUS REGULATORY REVIEW PROCESS THAN WE HAVE AT THE PRESENT TIME.</p>	<p>clinical outcomes. In fact, the case of rosiglitazone exemplifies why we should insist on clinical outcomes data.</p>
<p>Figures</p>	
<p>The text inside the figures is very small and hard to read and needs to be made bigger. The figures would benefit from inclusion of the raw data so that the reader can see upon which estimates are based. Particularly with the rare clinical outcomes, I suspect many of the estimates and confidence intervals are largely driven by the correction factor used for zero cell counts. The reader cannot appreciate these without seeing the data. Several programs exist for including the raw data in the forest plots.</p>	<p>We have corrected this.</p>
<p>They appear to be accurate and easy to read</p>	<p>Thank you for your comments.</p>
<p>Tables</p>	
<p>Comprehensive</p>	<p>Thank you for your comments.</p>
<p>Very thorough and an excellent resource for the reader</p>	<p>Thank you for your comments.</p>
<p>References</p>	
<p>On 10/5/2007, [Identifying information redacted] sent a scientific information packet to the AHRQ. Included in the packet were 37 references relevant to Key Questions. The following references are not included in the systematic review or in the Appendix C: List of Excluded Articles (pages C-1 through C-7). (see comments 24-26) [Identifying information redacted]</p>	<p>We have added these references to our list of exclusions.</p>

Scope	
A qualified yes. Perhaps this is being done in a separate AHRQ project (and there was a recent Cochrane review) of long acting analogs vs NPH.	Thank you for your comments.
General	
Many of the comparisons done appear to combine studies in which the comparison groups differ quite substantially, particularly with respect to whether the controls were used optimally in allowing dose titration. Thus, it seems as if many of the positive results found may be misleading. Some type of meta-regression would be desirable, although the number of studies is usually too small. An alternative might be to more clearly indicate in figures those studies in which the comparison involves a control not used as in usual clinical practice.	We agree with the reviewer that the studies in comparison groups were not quite similar to each other. Due to the heterogeneity in the studies within a comparison group, we have presented results first qualitatively and then quantitatively, thus highlighting the differences between the studies.
For usability, it might help to have hyperlinks embedded within the document from key conclusions to specific evidence tables.	Thank you for your comments.
The authors ought to be congratulated for putting together a large body of complex and diverse literature in a lucid document.	Thank you for your comments.
Page C-1: In some of the excluded references like 12 and 13, the last two digits of the year are missing.	We have made this correction.
Do the authors believe there is an important difference when studies use "blood glucose" or "plasma glucose" (such as the Herz study noted on page 47)? Can these two types of glucose (blood and plasma) measurements be compared equally to each other, and across studies?	Self-monitored blood glucose levels accurately reflect plasma glucose (see Saudek et al; JAMA 2006). To highlight this fact, we have added a sentence in the Methods section of the report with a reference to literature.
Overall presentation and relevancy	
In general, I found this report very difficult to read. There were so many results and so much text that it was hard to process. I think the report could benefit from some more tables and figures summarizing results. I indicate these in my comments below.	We have added tables and a figure to present results concisely. As the reviewer has pointed out in another comment below, the studies within comparisons are quite often heterogeneous. Therefore, we presented results qualitatively before pooling the studies. This qualitative description of studies may appear as too much text.
Should be highly relevant to clinicians and formularies, and should provide companies with a research agenda, especially as regards subpopulations	Thank you for your comments.