

### Comments to Research Review

The Effective Health Care Program encourages input on its projects. Comments and input may be submitted through several modes, including this Web site, letter, and e-mail. Comments to draft reports and the response to the comments will be posted publicly without attribution on this Web site 3 months after the reports are published. Comments are not edited for spelling, grammar, or other content errors.

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


### Comment, by Section

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<th>Executive Summary</th>
<th>Response</th>
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<td>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?. [Identifying information redacted] agrees and have completed a Phase III randomized controlled clinical trial ([Identifying information redacted]). The results were published in 2008. The citation is: [Identifying information redacted]</td>
<td>Thank you very much for this suggestion. We captured this article when we conducted an update of our literature search.</td>
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<td>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). Executive Summary doesn't include any Applicability findings.</td>
<td>We have corrected this inconsistency.</td>
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<td>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.</td>
<td>Thank you very much for your comment. We generally do not put references in the executive summary.</td>
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<td>Recommend changing &quot;effectiveness&quot; to &quot;efficacy&quot; since no observational studies were included in the systematic review.</td>
<td>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 &quot;effectiveness&quot; does not mean the same thing as including observational studies in a systematic review. According to the Draft Guide for Comparative effectiveness reviews, posted for public comments on AHRQ website, &quot;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.&quot;</td>
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<td>Rate of hypoglycemia was reported by different types of hypoglycemia (e.g., serious, daytime, nighttime) in the Evidence Table but not under Executive Summary.</td>
<td>Thank you for your suggestion. We have specified types of hypoglycemia in the executive summary.</td>
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<td>[Identifying information redacted] 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. [Identifying information redacted] is a biopharmaceutical company dedicated to improving patient lives through discovery, development and commercialization of innovative medicines. [Identifying information redacted] 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.</td>
<td>Thank you for your comments.</td>
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<td>[Identifying information redacted] 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. [Identifying information redacted] urges the Agency to make public its research questions, rationale for selecting those questions and how and to whom reports will be communicated</td>
<td>Thank you for your comments. AHRQ is responsible for the development of topic and key questions.</td>
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<tr>
<td>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.</td>
<td>Thank you for your comments.</td>
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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 relative to long-acting insulins potentially comes at the expense of added patient risk in terms of more hypoglycemic events and weight gain.

   We have pointed this out in the results section of the report.

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.

   Thank you for your comments.

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.

Thank you for your comments.

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.

We have mentioned this in the discussion section.

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 specific study populations evaluated may again limit the interpretation and generalizability of the findings.

We have mentioned this in the discussion section.

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.

Thank you very much for this suggestion. We captured this article when we conducted an update of our literature search.

References:

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..." 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.

Thank you. We have made appropriate changes as suggested.
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.

We have clarified this sentence.

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 or worse than
   exenatide (incretin mimic 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?

We have clarified this statement and separated exenatide in the key messages.

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?)

We have corrected this - it is “low”.

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

Yes, it is accurate.

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 whole blood or
plasma glucose measurements?

We have clarified this in the methods section, and made appropriate changes in rest of the report.

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.

We have clarified this sentence.

Specific edits within the documents

in a study of evidence-based medicine, this statement is unsupported by evidence. The addition of insulin
result in improved FLEXIBILITY of meals and activities, at least relative to some other medications (e.g.
sulfonylureas). So this blanket statement is not justified. Also, this statement only applies to certain 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.

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.

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 differentiated 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 results in "overall
patient satisfaction woth/ their treatment 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.

We have re-worded this sentence so that it now clearly reads as a hypothesis and not a conclusive statement.

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 amoung physicians and other health care providers, and
it is not a conclusion of the present study per se.

We have reworded this sentence to reflect that this is a mere suggestion and not an endorsement.

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.

We have included a definition of consistent meals with parenthesis.
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.

Thank you for pointing this out. We have clarified this sentence.

stictly 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.

We have changed to A1c throughout our report.

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 reason 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 misinterpreted. The authors need to indicate just what aspect of this kind of therapy is unclear, or presumably unclear, AND TO WHOM!

We have re-worded this sentence to make the comparison clear.

unclear - more than what? premixed with human regular insulin? or long acting? or MDI? it is unclear what the intended comparator is.

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.

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 this. This is something to address throughout the entire report to be sure that the reader clearly understands that this is "Regular or "R" insulin.

We have re-worded this sentence and removed 'newer' from the sentence and used 'alternative' instead of traditional to group other regimens.

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.

We have re-organized whole paragraph and addressed this concern.

does this mean alternative insulin, oral agents, oral + insulin, exenatide, or what. It is a bit vague. Does this study consider all of those?

We have clarified this sentence.

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?

As indicated when we present the Key Questions addressed in the report, we consider the three preparations as three separate premixed insulin analogues.

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 oevidence 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.

We have re-checked - 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.

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 therapies for thier prandial control, e.g. sulfonylureas, glinides, alphaglucosidase 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?

After updating report with additional studies, the results of this comparison are much more clear and we have re-written whole paragraph to reflect revised findings.

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 preparationn 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 ?)

We have re-organized whole paragraph and addressed this concern.

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.

We have clarified this.
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 should just say "basal bolus" and define that once, or use "MDI" referring to multiple daily injections."

We have reworded this sentence to make it more clear.

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 patient 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 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 oth er ways in which such funds could be spend on diabetes research.

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.

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 analogues, 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 timese 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.

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.

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 theTZDs. 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 ot 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.

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. We have reworded this sentence.

2) Background page 1; Second paragraph: “…regimens can be either near-physiologic….” We have changed physiologic with near-physiologic.

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. We have added a sentence to reflect timing of the insulin injections.

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. We have removed the sixth condition - we agree with the reviewer.

5) Page 5 and in the Executive Summary Page ES -2: Key question 1 item e: Rapid acting insulin analogues…with a long- or intermediate acting insulin analogues”. Detemir is often a twice a day preparation. The same comments apply to the body of the text. 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.

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 or regular human insulin…with an intermediate acting NPH human insulin". Key questions were decided quite early in the process with the mutual consensus of AHRQ and EPC team. 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.

### Methods
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. This is an excellent suggestion and we had thought about performing sensitivity analysis in several different ways. 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.

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" 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. Thank you very much for bringing up this concern. We had always considered quality of life as being a part of the key 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.

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): We have included a separate section on adherence in the results section.

Treatment allocation procedure and blinding information are enclosed in the Evidence Table but not in the text under Methods. 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.

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? 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.

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. This is a good suggestion. We believe that AHRQ is developing a methods manual for comparative effectiveness reviews and we hope that it will outline in detail why certain methods are used in certain situations.

I am not an expert of biostatistics but as far as I can tell the statistical methods used and the metanalytical approach is correct. Thank you for your comments.

Very thorough and superb attention to detail. Thank you for your comments.

Study selection page 8: Title reviews may overlook some studies. What key words were used in the title review? Insulin analogue, diabetes control? A sentence clarifying this has been added to the Study Selection section in the Methods chapter.

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 part of Key Questions. We recommend inserting "quality of life" 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.

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 the summary too long and we 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). We have rechecked it and data as stated in the report is correct.

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.

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 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, 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.

We have reworded this sentence to reflect no difference in patients with A1c less than 8.6.

Insulin Lispro 75/25 versus Long-acting insulin analogues
1. On page 43, the statement that insulin Lispro 75/25 more effectively lowered overnight post-prandial 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.

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).

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.

Insulin Aspart 70/30 versus Long-acting insulin analogues
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.

We have reworded this sentence to reflect no difference in patients with A1c less than 8.6.

Insulin Lispro 50/50 versus Long-acting insulin analogues
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.

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.

Too many words and not enough concise use of tables and figures
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 "+" sign or empty 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 information. 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 repetitious. You might also consider separate tables for the different preparations (see comment above on potential inconsistencies in conclusions for the different premixed formulations). We have added such a figure.

Page 27, line 4: Should be "the remaining three studies …." Thank you, we have corrected it.

Page 38: Please provide logic behind exclusion of study by Nauck in figures We have added a sentence to provide logic behind the analyses done with and without Nauck et al.

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 …"
<table>
<thead>
<tr>
<th>Comment</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, The introduction and conceptual framework was nicely done. Including the Holman study and showing the results with and without it strengthens the review.</td>
<td>Thank you for your comments.</td>
</tr>
<tr>
<td>Comprehensive</td>
<td>Thank you for your comments.</td>
</tr>
<tr>
<td>1) Page 24: Hypoglycemia (also Appendix E: Evidence Table 1) The body of evidence was graded &quot;high&quot; for certain comparisons. I would grade that as &quot;moderate&quot; 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.</td>
<td>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.</td>
</tr>
<tr>
<td>2) Page 25: Describing study characteristics it would be helpful to know to what degree these studies achieved glycemic goals.</td>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
<td>Thank you, we have corrected it.</td>
</tr>
<tr>
<td>4) Page 27: The fact that the study by Holaman et al was funded by [Identifying information redacted] is stated. What was the contribution of [Identifying information redacted] to the study of [Identifying information redacted]? This issue of the source of funding is covered in the section on Study Quality Assessment on page 58.</td>
<td>We have included all mention to the source of funding to the relevant sections and removed it from the main section of the results.</td>
</tr>
<tr>
<td>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.</td>
<td>Thank you, throughout the report we have referred the reader to the evidence tables where needed.</td>
</tr>
<tr>
<td>Can evidence ratings be assigned for all Level of Evidence (LOE) statements rated as “not stated” in the Key Messages?</td>
<td>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.</td>
</tr>
<tr>
<td>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.) 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.</td>
<td>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. We have provided values of binary variables either in the text or in the figures in the results section.</td>
</tr>
<tr>
<td>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.</td>
<td>No, for exenatide, there was no difference between the two groups. We have made few changes to key messages to further clarify this fact.</td>
</tr>
<tr>
<td>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</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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.

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. Thank you - please see comment above.

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. Thank you for your comments.

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.

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).


Limitations:

We suggest addressing the potential impact of several methodological issues on the results and interpretation of comparator trials with respect to the following:

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.

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.

3. Titration method: In a number of the studies (Malone 2004, Malone 2005, Jacober 2006, 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.

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 [Identifying information redacted] 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: [Identifying information redacted]

We have pointed out this limitation of the studies in the Discussion section.

1) Study Title: 52-Week, Open, Randomized, Multinational, Multicenter Clinical Trial Comparing Insulin Glulisine in Combination With Insulin Glargine in an Intensified Insulin Regimen to a Two-Injection Conventional Insulin Regimen in Type 2 Diabetes Mellitus Patients With Poor Glycemic Control Pretreated With a Two-Injection Conventional Insulin Therapy (GINGER: Insulin glulisine in diabetes mellitus, type 2) ClinicalTrials.gov Identifier: NCT00174668

Treatment period: 52 weeks

Objective: The primary study objective is to demonstrate superior efficacy of an intensified insulin regimen with insulin glulisine and insulin glargine to a two-injection premixed insulin regimen

Study start: November 2004

Study data will be available during Q3 2008

We have updated this systematic review and have included the study by Rosenstock et al.

We have pointed out these two issues in the Discussion section of the report.

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.

We have added this limitation under the subheading of limitations in the Discussion section of the report.

We have added this limitation while reviewing the key findings and clinical implications.

We have added this limitation in the results section while reviewing the key findings and clinical implications.

We have added this limitation in the Discussion section while reviewing the key findings and clinical implications.

We have pointed out this systematic review and have included the study by Rosenstock et al.
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.


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 [Identifying information redacted] and described above ([Identifying information redacted]) 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.

Thank you for your comments.
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.

Figures
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.
They appear to be accurate and easy to read
Thank you for your comments.

Tables
Comprehensive
Thank you for your comments.

Very thorough and an excellent resource for the reader
Thank you for your comments.

References
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)

We have added these references to our list of exclusions.


We have added these references to our list of exclusions.


We have added these references to our list of exclusions.


We have added these references to our list of exclusions.

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.