Evidence-based Practice Center Systematic Review Protocol

Project Title: *Comparative Effectiveness and Safety of Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update of the 2007 Report*

I. Background and Objectives for the Systematic Review

Type 2 diabetes is increasing in the United States and has a high burden of morbidity and mortality.[1-3] Management of type 2 diabetes is complex and involves recommendations for weight management and exercise, glycemic control using a variety of medications, and lowering co-morbid cardiovascular disease risk factors.[4] Studies suggest that improved glycemic control reduces microvascular complications,[1, 5-8] but the impact on cardiovascular disease risk is less clear.[1, 5, 8, 9]

There are numerous medications approved for the treatment of type 2 diabetes. To better understand the comparative effectiveness of oral medications for adults with type 2 diabetes, we conducted a Comparative Effectiveness Review (CER) commissioned by the Agency for Healthcare Research and Quality (AHRQ) in 2007.[10] One important finding from the report highlighted the effectiveness of metformin, as compared with newer, more expensive agents, in the treatment of type 2 diabetes. Since the publication of the report, two new therapeutic classes arrived on the market, the dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin) and incretin mimetics (e.g., exenatide). There is also new evidence and concern about risks and benefits associated with thiazolidinediones,[11, 12] which was not systematically assessed in the original report.

In addition to updating the 2007 CER and refining its key questions, this review responds to a nomination to AHRQ to compare the effectiveness and safety of 2nd line therapies for adults with type 2 diabetes. It addresses both monotherapy and combination therapy for the management of type 2 diabetes in adults. See Figure 1 for the Analytic framework for this CER.

II. The Key Questions

Key Question 1: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (see Tables 1 and 2 for lists of comparisons) for the intermediate outcomes of glycemic control (in terms of HgbA1c), weight, or lipids?

Key Question 2: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options (see Tables 1 and 2 for list of comparisons) in terms of the following long-term clinical outcomes?

- All-cause mortality
- Cardiovascular mortality
- Cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke)
- Retinopathy
- Nephropathy
- Neuropathy

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Key Question 3: In adults age 18 or older with type 2 diabetes mellitus, what is the comparative safety of the following treatment options (see Tables 1 and 2 for a list of comparisons) in terms of the following adverse events and side effects?

- Hypoglycemia
- Liver injury
- Congestive heart failure
- Severe lactic acidosis
- Cancer
- Severe allergic reactions
- Hip and non-hip fractures
- Pancreatitis
- Cholecystitis
- Macular edema or decreased vision
- Gastrointestinal (GI) side effects

Key Question 4: Do safety and effectiveness of these treatment options (see Tables 1 and 2 for a list of comparisons) differ across subgroups of adults with type 2 diabetes, in particular for adults age 65 or older, in terms of mortality, hypoglycemia, cardiovascular and cerebrovascular outcomes?

PICOTS

Population(s)

The population will include non-pregnant adults age 18 or older with type 2 diabetes mellitus.

Interventions

The interventions will include oral diabetes medications as first line and second line therapy. First-line therapy would include metformin, thiazolidinediones (rosiglitazone and pioglitazone), second-generation sulfonylureas (glimepiride, glipizide, and glyburide), sitagliptin, and the meglitinides (repaglinide and nateglinide). Second-line therapy would include combinations of metformin and a thiazolidinedione, a sulfonylurea, a meglitinides, sitagliptin, exenatide, a basal insulin, or a premixed insulin.

Comparators

See Tables 1 and 2 for a list of comparisons.

Outcomes for each question

The outcomes for Key Question 1 are:

- HgbA1c
- Weight
- Low density lipoprotein
- High density lipoprotein
- Triglycerides

The outcomes for Key Question 2 are:

- All-cause mortality
- Cardiovascular mortality
- Cardiovascular and cerebrovascular morbidity (e.g., myocardial infarction and stroke)
- Retinopathy
- Nephropathy
- Neuropathy

The outcomes for Key Question 3 are:

- Hypoglycemia
- Liver injury
- Congestive heart failure
- Severe lactic acidosis
- Cancer
- Severe allergic reactions
- Hip and non-hip fractures
- Pancreatitis
- Cholecystitis
- Macular edema or decreased vision
- Gastrointestinal (GI) side effects

Key Question 4 considers all of the outcomes.

Timing

We will include studies if patients have been on the medications for at least 3 months.

Settings

We will have no exclusions based on study setting.

III. Analytic Framework

Figure 1 describes our analytic framework. It starts with the diagnosis of type 2 diabetes. The diagnosis of type 2 diabetes leads to initial medical treatment. There are several options for initial medical treatment, including: dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin); thiazolidinediones (TZD; e.g., rosiglitazone and pioglitazone); biguanides (e.g., metformin and metformin XR); second generation sulfonylureas (e.g., glyburide and glipizide); and meglitinides (e.g., repaglinide).

After initial medical treatment has begun, hemoglobin A1c is tested. If hemoglobin A1c is greater than or equal to 7.0 percent, then a second agent is added. Second line agents include: the addition of a second oral medication (such as a DPP-4 inhibitor added to metformin, a sulfonylurea, or a TZD; metformin added to a TZD or a sulfonylurea; or a sulfonylurea added to a TZD); the addition of insulin (such as a basal insulin, e.g., NPH insulin, insulin glargine, or insulin detemir) to metformin, a sulfonylurea, a TZD, or a DPP-4 inhibitor; the addition of a premixed insulin (e.g., premixed human insulin 70/30, premixed human insulin 75/25, premixed

insulin analogue 70/30, and premixed insulin analogue 75/25) to metformin, a sulfonylurea, a TZD, or a DPP-4 inhibitor; or the addition of exenatide to metformin, a sulfonylurea, a TZD, or a DPP-4 inhibitor.

For both initial medical treatment and the addition of a second line agent, outcomes will be measured. Outcomes include intermediate outcomes, long-term outcomes, safety, adverse events, mortality, and quality of life and functional status. Intermediate outcomes are glycemic control, serum lipid levels, weight, and blood pressure. Long-term outcomes can be classified as macrovascular complications (such as incident coronary artery disease and events, peripheral vascular disease and amputations, and stroke) and microvascular complications (such as retinopathy, nephropathy, and neuropathy). Adverse events include congestive heart failure, hypoglycemia, pancreatitis, fractures, and cancer.

The effect of initial and second-line medical treatment on outcomes can be modified by age, race, sex, medical comorbidity, and medication adherence.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The inclusion and exclusion criteria (Table 3) for this review will be similar to that of the initial CER, with a few exceptions. First, this review will include interventions that were excluded from the initial CER: sitagliptin, combination metformin plus sitagliptin, combination metformin plus a meglitinide, combination metformin plus exenatide, combination of metformin plus a basal insulin, combination of metformin plus a premixed insulin, and combination thiazolidinedione plus a meglitinide. This review will include studies with unambiguous medication combinations but not studies in which participants were treated with unspecified adjunctive diabetes medications. Second, this review will include outcomes that were not included in the initial CER: fractures, cholecystitis, and macular edema. We will not update the initial CER on the outcomes of blood pressure, body mass index, 2-hour postprandial glucose, peripheral arterial disease, amputations, quality of life, functional status, anemia, thrombocytopenia, leucopenia, hypervolemia, and withdrawals due to adverse events.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will search the following databases for primary studies: MEDLINE®, EMBASE®, and the Cochrane Central Register of Controlled Trials. We will develop a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori. Our search strategy will be similar to the one used for the initial 2007 CER,[10] but it will include terms for the additional medications included in this review (e.g., sitagliptin).

In addition, we will review the Scientific Information Packets provided by the pharmaceutical manufacturers. We will hand search 15 journals that are most likely to publish articles on this topic by scanning the table of contents of each issue for relevant citations. We will also review the reference lists of each included article and relevant review articles.

C. Data Abstraction and Data Management

Two independent reviewers will conduct title scans in parallel. For a title to be eliminated at this level, both reviewers will need to indicate that it was ineligible. If they disagree, the article will be promoted to the next level.

The abstract review phase was designed to identify studies reporting the effects of oral diabetes medications on intermediate outcomes, long-term clinical outcomes, or adverse events and side effects. Abstracts will be reviewed independently by two investigators, and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 3). Differences between investigators regarding abstract inclusion or exclusion will be resolved through consensus adjudication.

Articles promoted on the basis of abstract review will undergo another independent parallel review to determine if they should be included for data abstraction. Differences regarding article inclusion will be resolved through consensus adjudication.

D. Assessment of Methodological Quality of Individual Studies

Article quality will be assessed differently for randomized controlled trials (RCTs) and observational studies. For RCTs the dual, independent review of article quality will be based on the Jadad criteria: (1) appropriateness of the randomization scheme, (2) appropriateness of the blinding, and (3) description of withdrawals and drop-outs.[13] For the updated review, we will also include a question to evaluate the overall quality of the study, as suggested by the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[14]

We will develop a quality assessment tool for observational studies based on the recommendations in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews[14] and quality forms previously developed by our Evidence-based Practice Center.[15] The quality assessment will include items about the study setting, inclusion and exclusion criteria, key characteristics of enrolled subjects, details about the treatments, details about the outcomes and how they were measured, statistical analysis, losses to followup, and the overall study quality. For both the RCTs and the observational studies, the overall study quality will be assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to the commonly held concepts of high quality, including the following: a formal randomized controlled design; a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.
- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of good quality because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.[14]

In the initial 2007 CER, we did not assess the quality of observational studies or non-randomized trials.

E. Data Synthesis

We will conduct meta-analyses when there are sufficient data (at least 3 trials) and studies are sufficiently homogenous with respect to key variables (population characteristics, study duration, and drug dose).

F. Grading the Evidence for Each Key Question

At the completion of our review, we will grade the quantity, quality and consistency of the best available evidence addressing Key Questions 1, 2 and 3 by adapting an evidence grading scheme recommended by the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews.[14] We will apply evidence grades to the bodies of evidence about each intervention comparison for each outcome. We will assess the strength of the study designs with RCTs considered best, followed by non-RCTs, and observational studies. We will assess the quality and consistency of the best available evidence, including assessment of limitations to individual study quality (using individual quality scores), consistency, directness, precision, and the magnitude of the effect.

We will classify evidence pertaining to Key Questions 1, 2 and 3, into four basic categories: (1) “high” grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) “moderate” grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) “low” grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) “insufficient” grade (evidence is unavailable).

V. References

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VI. Definition of Terms

Not applicable

VII. Summary of Protocol Amendments

04-02-2010 Amendment I

Including Drugs Recently Approved by the U.S. Food and Drug Administration

In response to comments received on the posted Key Questions, the following changes will be made to the protocol. The search and protocol will be updated to include all FDA-approved drugs and indications, as of March 31, 2010. This will include the DPP-IV inhibitor saxagliptin, which was FDA-approved in July 2009. Thus there will be two included DPP-IV inhibitors: sitagliptin and saxaglitpin. The GLP-1 agonist, liraglutide, was just FDA approved in January 2010, for both mono- and combination therapy and both indications will be included. In addition, the GLP-1 agonist exenatide was approved for the indication of monotherapy, in addition to combination therapy, which had already been included in the protocol.

Revisions to the protocol will include adding these monotherapy and combination therapy comparisons in Figure 1 and Tables 1-3.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

The key questions were reviewed and refined by the EPC and the Technical Expert Panel (TEP). They were later posted for public comment.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

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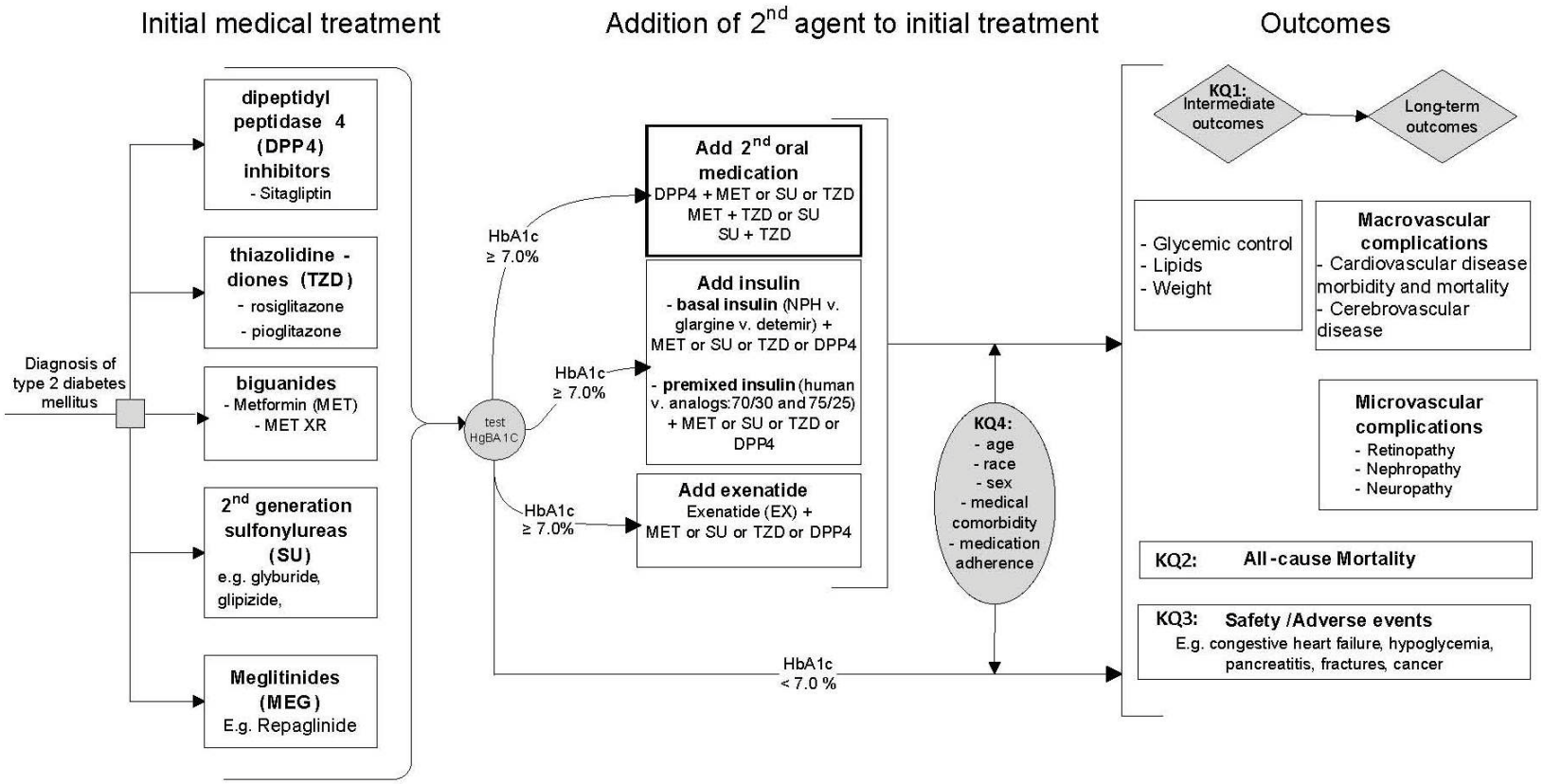
Figure 1. Analytic Framework



HgbA1c = hemoglobin A1c; KQ = Key Question; NPH = neutral protamine Hagedorn

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Figure 1 Narrative

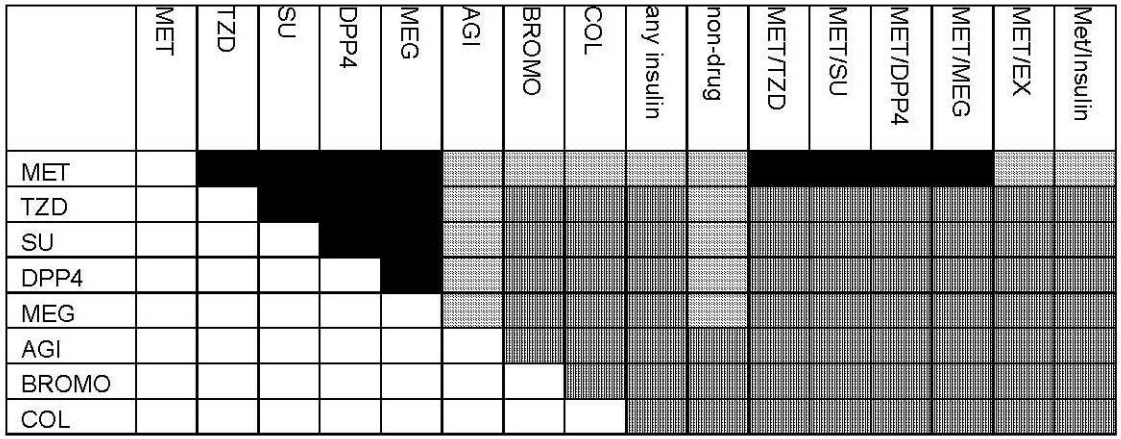
Figure 1 describes our analytic framework. It starts with the diagnosis of type 2 diabetes. The diagnosis of type 2 diabetes leads to initial medical treatment. There are several options for initial medical treatment, including: dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin); thiazolidinediones (TZD) (e.g., rosiglitazone and pioglitazone); biguanides (e.g., metformin and metformin XR); second generation sulfonylureas (e.g., glyburide and glipizide); and meglitinides (e.g., repaglinide).

After initial medical treatment has begun, hemoglobin A1c is tested. If hemoglobin A1c is greater than or equal to 7.0%, then a second agent is added. Second line agents include: the addition of a second oral medication (such as a DPP-4 inhibitor added to metformin, a sulfonylurea, or a TZD; metformin added to a TZD or a sulfonylurea; or a sulfonylurea added to a TZD); the addition of insulin (such as a basal insulin, e.g., NPH insulin, insulin glargine, or insulin detemir) to metformin, a sulfonylurea, a TZD, or a DPP-4 inhibitor; the addition of a premixed insulin (e.g., premixed human insulin 70/30, premixed human insulin 75/25, premixed insulin analogue 70/30, and premixed insulin analogue 75/25) to metformin, a sulfonylurea, a TZD, or a DPP-4 inhibitor; or the addition of exenatide to metformin, a sulfonylurea, a TZD, or a DPP-4 inhibitor.

For both initial medical treatment and the addition of a second line agent, outcomes will be measured. Outcomes include intermediate outcomes, long-term outcomes, safety, adverse events, mortality, and quality of life and functional status. Intermediate outcomes are glycemic control, serum lipid levels, weight, and blood pressure. Long-term outcomes can be classified as macrovascular complications (such as incident coronary artery disease and events, peripheral vascular disease and amputations, and stroke) and microvascular complications (such as retinopathy, nephropathy, and neuropathy). Adverse events include congestive heart failure, hypoglycemia, pancreatitis, fractures, and cancer.

The effect of initial and second-line medical treatment on outcomes can be modified by age, race, sex, medical comorbidity, and medication adherence.

Table 1. Monotherapy comparisons considered for review



Black boxes indicate comparisons that were included in the review; boxes with diagonal lines indicate comparisons that were not included, but tallied; and boxes with a grid indicate comparisons that were excluded from the review.
AGI = alpha-glucosidase inhibitors; BROMO – bromocriptine; COL = colesevalam; DPP4 = dipeptidyl peptidase-4 inhibitors; MEG = meglitinides; MET = metformin; SU = sulfonylurea; TZD = thiazolidinedione

Table 1 Narrative

Table 1 displays the monotherapy comparisons being considered for our review. In the left-most column, we list the possible monotherapy interventions for type 2 diabetes: metformin, thiazolidinediones (TZDs), sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, alpha-glucosidase inhibitors, bromocriptine, and colesevalam. Across the top are listed the possible comparators. In addition to the possible interventions, the comparators include any insulin, non-drug interventions, and combinations of metformin with TZDs, sulfonylureas, DPP-4 inhibitors, meglitinides, exenatide, or insulin. For each possible comparison, we indicate if it should be included, not included but tallied, or excluded from the review.

Comparisons we are considering for inclusion are head-to-head comparisons of metformin, TZDs, sulfonylureas, DPP-4 inhibitors, and meglitinides. We are also considering including comparisons between metformin and combinations of metformin with TZDs, sulfonylureas, DPP-4 inhibitors, or meglitinides.

We are proposing to tally, but not include, studies that compare metformin with one of the following interventions:

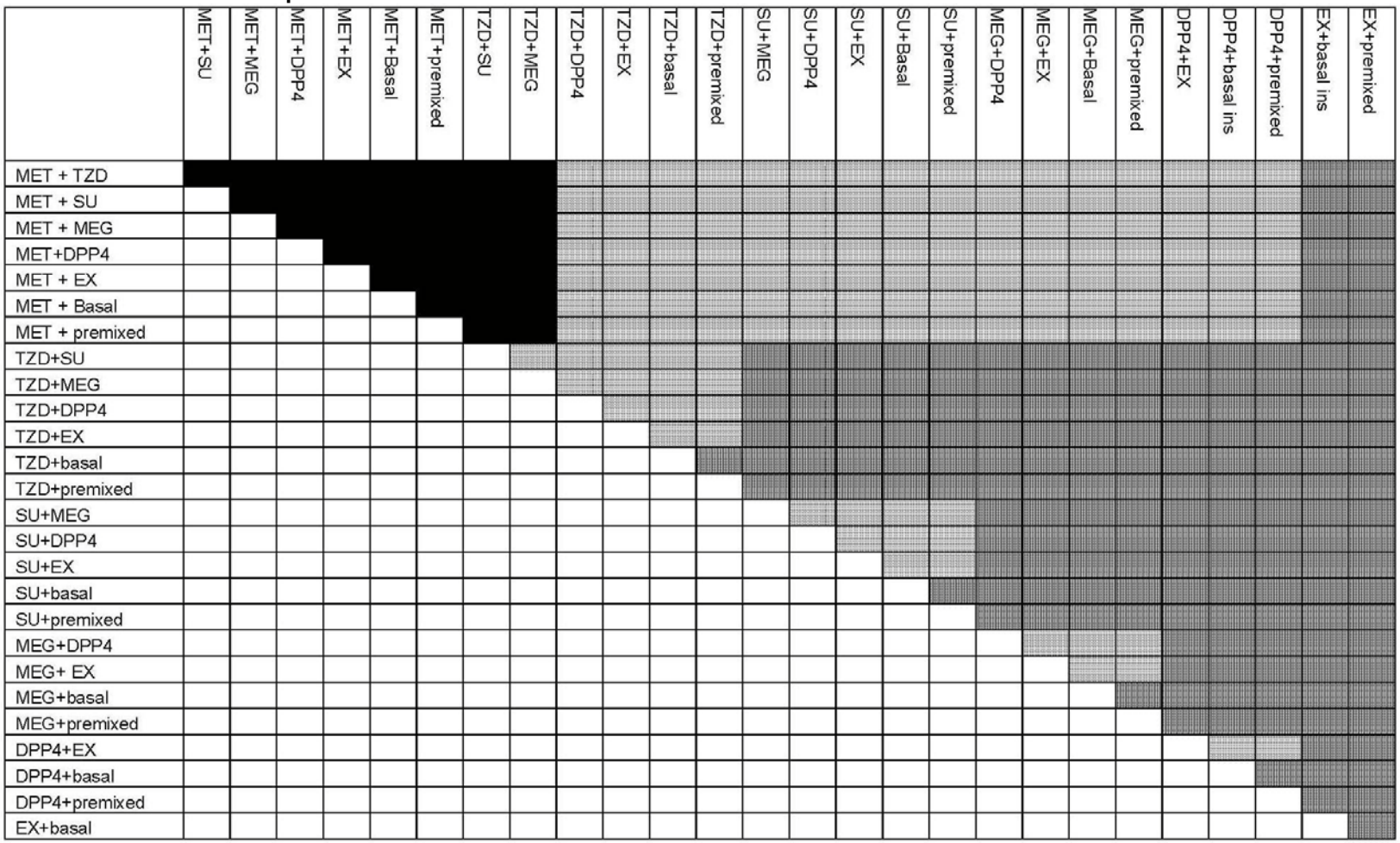
- Alpha-glucosidase inhibitors,
- Bromocriptine,
- Colesevalam,
- Any insulin,
- Non-drug interventions,
- Combination of metformin and exenatide, and
- Combination of metformin and insulin.

We also plan to tally studies that compare either an alpha-glucosidase inhibitor or a non-drug intervention to one of the following:

- TZDs,
- Sulfonylureas,
- DPP-4 inhibitors, and
- Meglitinides.

We are planning to exclude all other monotherapy comparisons.

Table 2. Combination comparisons considered for review



Black boxes indicate comparisons that were included in the review; boxes with diagonal lines indicate comparisons that were not included, but tallied; and boxes with a grid indicate comparisons that were excluded from the review.
AGI = alpha-glucosidase inhibitors; basal = basal insulin; BROMO – bromocriptine; COL = colesevalam; DPP4 = dipeptidyl peptidase-4 inhibitors; EX = exenatide; MEG = meglitinides; MET = metformin; premixed = premixed insulin; SU = sulfonylurea; TZD = thiazolidinedione

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Table 2 Narrative

Table 2 displays the combination comparisons being considered for our review. The combinations of type 2 diabetes medications considered for this review are listed along the side and the top of the table. The combinations include one of the following drugs:

- Metformin,
- Thiazolidinediones (TZDs),
- Sulfonylureas,
- Meglitinides,
- Dipeptidyl peptidase-4 (DPP-4) inhibitors, and
- Exenatide

Combined with one of the following medications:

- TZDs,
- Sulfonylureas,
- Meglitinides,
- DPP-4 inhibitors,
- Exenatide,
- Basal insulin, and
- Premixed insulin.

For each possible comparison of combinations, we indicate if it should be included, not included but tallied, or excluded from the review.

We are considering including head-to-head comparisons of the following combinations:

- Metformin and TZD,
- Metformin and sulfonylureas,
- Metformin and meglitinides,
- Metformin and DPP-4 inhibitors,
- Metformin and basal insulin, and
- Metformin and premixed insulin.

We are also considering for inclusion studies that compare one of the metformin combinations mentioned above with a TZD combined with either a sulfonylurea or a meglitinde.

We are tallying, but not including, studies that compare the metformin combinations mentioned above with the following combinations:

- TZD and either a DPP-4 inhibitor, exenatide, basal insulin, or a premixed insulin,
- Sulfonylurea and one of the other diabetes medications,
- Meglitinides and one of the other diabetes medications, and
- DPP-4 inhibitors and one of the other diabetes medications.

We are also tallying studies that evaluate the following comparisons:

- Combination of a TZD and either a sulfonylurea, meglitinide, DPP-4 inhibitor, or exenatide versus a combination of a TZD and one of the other diabetes medications,
- Combination of a sulfonylurea and either a meglitinde, DPP-4 inhibitor, or exenatide versus a combination of a sulfonylurea and one of the other diabetes medications,
- Combination of a meglitinide and either a DPP-4 inhibitor or exenatide versus a combination of a meglitinide and one of the other diabetes medications, and

- Combination of a DPP-4 inhibitor and exenatide and one of the other diabetes medications.

We are excluding all other comparisons of combination therapies from this review.

Table 3. Inclusion and exclusion criteria

Population and condition of interest	☐ All studies included patients with type 2 diabetes, non-insulin dependent diabetes mellitus, or adult-onset diabetes. We excluded studies that evaluated only patients with type I diabetes, impaired glucose tolerance, metabolic syndrome, maturity onset diabetes of youth, and gestational diabetes. ☐ All studies included human subjects. ☐ We excluded studies if they included only pregnant women or only subjects ≤18 years of age.
Interventions	☐ All studies must have evaluated an oral diabetes medication or drug combination of interest. o Biguanides (metformin) o Thiazolidinediones (rosiglitazone, pioglitazone) o Second-generatoin sulfonylureas (glyburide, glibenclamide, glipizide, glimepiride) o Dipeptidyl peptidase-4 inhibitor (sitagliptin) o Meglitinides(repaglinide, nateglinide) o Combination of metformin plus a thiazolidinedione o Combination of metformin plus a sulfonylurea o Combination of metformin plus sitagliptin o Combination of metformin plus a meglitinide o Combination of metformin plus exenatide o Combination of metformin plus a basal insulin (insulin glargine, insulin detemir, NPH insulin) o Combination of metformin plus a premixed insulin (NPH/regular 50/50, NPH/regular 70/30, insulin lispro 50/50, insulin lispro 75/25, insulin aspart 70/30) o Combination of a thiazolidinedione and a sulfonylurea o Combination of a thiazolidinedione and a meglitinide ☐ We excluded studies that did not specify the adjunctive medications, such as those stating use of “any oral hypoglycemic” or if the study listed possible medications without stratification of the results by treatment.
Comparisons of interest	☐ We excluded studies that did not have a comparison group. ☐ Table 2 presents the diabetes medication comparisons of interest. We excluded studies that did not have one of these comparisons.
Outcomes	☐ We excluded studies that did not apply to the key questions. ☐ For Key Question 1, we included the following outcomes: HgbA1c, weight, and serum lipid levels (HDL, LDL, TG). o We did not include data on total cholesterol or other measures of glycemic variability. ☐ For Key Question 2, we included the following outcomes: all-cause mortality, cardiovascular disease mortality, cardiovascular and cerebrovascular disease morbidity, retinopathy, neuropathy, and nephropathy. o We excluded biologic markers of outcomes, such as vascular endothelial function or carotid intima medial thickness. ☐ For Key Question 3, we included the following outcomes: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and non-hip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and GI side effects.
Type of study	☐ We excluded articles not written in English, studies less than 3 months in duration, studies with less than 40 total subjects, articles with no original data (editorials, comments, letters). ☐ For Key Question 1, we included only RCTs. ☐ For Key Questions 2 and 3, we included only RCTs, non-RCTs, cohort studies with a comparison group, and case-control studies. ☐ We included crossover studies for the outcomes of hypoglycemia, liver injury, and GI side effects regardless of the duration of the washout period. For all other outcomes, we included crossover studies only if the the washout period was > 1 month.

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GI = gastrointestinal; HDL = high density lipoprotein; HgbA1c = hemoglobin A1c; LDL = low density lipoprotein; NPH = neutral protamine Hagedorn; RCT = randomized controlled trial; TG = triglycerides

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