

Evidence-based Practice Center Systematic Review Protocol

Project Title: *Therapies for Children with Autism Spectrum Disorders*

I. Background and Objectives for the Systematic Review

Background

Autism Spectrum Disorders (ASD) are among the most common neurodevelopmental disorders, with an estimated prevalence of 6.7 cases per 1,000 children aged 8 years.¹ The etiology of ASD is largely unknown, but likely includes a genetic component. Consistent biomarkers or environmental triggers have not been identified; although factors ranging from oxidative stress, advanced parental age, and prenatal drug exposure, among others, have been investigated.²

Disorders within the autism spectrum include Autistic Disorder, Asperger's Syndrome, and Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS). Rett Syndrome and Childhood Disintegrative Disorder are included in the Pervasive Developmental Disorders category but are typically considered as separate from the Autism Spectrum Disorders. ASD are characterized by significant impairments in social interaction, behavior, and communication.³ Impairments include a lack of reciprocal social interaction and joint attention; dysfunctional or absent communication and language skills; lack of spontaneous or pretend play; intense preoccupation with particular concepts or things; and repetitive behaviors or movements. Children with ASD may also exhibit impaired cognitive skills and sensory perception.^{1,3} ASD is often accompanied by comorbid conditions such as seizure disorders, hyperactivity, and anxiety.⁴

The manifestation and severity of symptoms of ASD differ widely, and treatments comprise a range of behavioral, psychosocial, educational, medical, and complementary approaches⁵⁻⁷ that vary given a child's age and developmental status. Goals of treatment often focus on alleviating core deficits in communication, social interactions, or behavior and must take into account a child's developmental context; however treatment is frequently complicated by emergent symptoms such as irritability and other common co-morbid conditions. Given the complexity of ASD and associated therapies, clinicians and families need guidance in selecting appropriate treatments. There is no cure for autism spectrum disorders and no global consensus regarding which intervention strategy is most effective. Chronic management is often required, and the goals of treatment are to maximize the child's ultimate functional independence and quality of life by minimizing the core autism spectrum disorder features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. Early, appropriate, and sustained behavioral and educational intervention may be associated with improved short-term outcomes and quality of life, although specific strategies vary. Management strategies consist of a diverse set of interventions that vary in their modality; many lack a systematic evidence base and are instead supported by small case series, single cases, or small, short-term trials.

Previous reviews of the literature have noted limited quality and consistency in studies assessing ASD therapies,^{6, 8-12} and an umbrella review found methodological weaknesses in systematic reviews of psychosocial interventions.⁷ While controlled trials seem to be increasing, much research is observational, generally with small sample sizes, limited follow-up, and limited discussion of the durability of treatment gains once active therapy ends. As the prevalence of ASD has increased, the available treatment options have also increased, but evidence overall for many interventions can only be considered preliminary. It is clear that there is a real need for synthesized research that evaluates the evidence base for various treatments and identifies gaps in the current literature that may drive the research agenda.

While advances have been made in early diagnosis and the promotion of early intervention for ASD, there are no current guidelines for comparing the benefits and harms of treatment interventions. Clinicians and families are left to choose among the interventions in part based on what is available to them, what is covered by commercial insurance or Medicaid, or what they can afford out of pocket. The bottom line is that parents and caregivers are not given consistent advice on how to treat and manage this condition. Often, clinical recommendations are based on the most common or most popular treatments at a given time. Many therapies are not covered by insurance, and a primary reason for insurance denial from private insurers is that there are no evidence-based guidelines for this condition. Additionally, insurers may find it confusing to distinguish among therapies or to sort out which approaches have an evidence base and which are still experimental.

The delivery and organization of care for ASD is very fragmented, with pieces scattered about in the primary care, school, and specialty clinical settings. It is left to the families and caregivers of patients with ASD to find and assemble these pieces. Patients and caregivers are ultimately left with a “laundry list” of treatment and management strategies that appear to have equal weighting, without prioritization among the choices. This situation presents many challenges not only to patients and families, but also to health policy and decision makers.

Nominations for a comprehensive systematic review of therapies for ASD, submitted by a member of the Medicaid Medical Director’s Learning Network and on behalf of the Autism Speaks advocacy organization, emphasized the need to understand the effectiveness and comparative effectiveness of various treatment modalities.

FDA Approved Treatments. At present only Risperdal is approved by the FDA for treating irritability associated with autistic disorder in children aged 5-16 years.

II. The Key Questions

Introduction

Comments on the posted key questions will be used in framing the report, but did not warrant any changes in the questions themselves. Comments that supported the expansion of questions or the addition of additional areas of research were consolidated for AHRQ as potential additional reviews. Recommendations were made to a) specifically address the treatment of co-morbid conditions and b) to conduct a parallel review on therapies for adolescents in particular.

Individuals also made comments requesting assurance that the review would both attempt to isolate individual treatment components, and assess the impact of combinations of therapies. Our

intent is to regard those combination treatments that are evaluated as such in the literature as unique treatment modalities. In addition, Key Question 5 specifically addresses the question of effectiveness of individual components of combination treatments. As written, the review will include attempts to isolate individual effects where those data are available.

Additional comments related to the need to understand modifiers of treatment effects. As is our usual method, we will begin by establishing a list of modifiers a priori that are expected in the literature in order to identify both presence and absence of those variables in current research. We will further capture data on additional modifiers as they are available in the research.

Finally, one reviewer recommended that we capture information on funding source. Funding source could refer either to research funding or to payment data for clinical care. We will explicitly capture data on the funding source of the research and on any additional funding information provided as it relates to payment for therapies or treatments.

After our first Technical Expert Panel (TEP) discussion on October 1, 2009, we revised the key questions to clarify the emphasis on examining the correlation of early treatment phase indicators with outcomes; correlation of short-term, targeted outcomes with longer-term functional outcomes; and the generalizability of effects beyond the immediate treatment conditions. Key questions 3-5 address these aspects.

Key Questions

KQ1: Among children ages 2-12 with ASD, what are the short and long-term effects of available behavioral, educational, family, medical, allied health, or CAM treatment approaches? Specifically,

KQ1a: What are the effects on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors), in the short term (≤ 6 months)?

KQ1b: What are the effects on commonly associated symptoms (e.g. motor, sensory, medical, mood/anxiety, irritability, and hyperactivity) in the short term (≤ 6 months)?

KQ1c: What are the longer-term effects (> 6 mos) on core symptoms (e.g. social deficits, communication deficits and repetitive behaviors)?

KQ1d: What are the longer-term effects (> 6 mos) on commonly associated symptoms (e.g. motor, sensory, medical, mood/anxiety, irritability, and hyperactivity)?

KQ2: Among children ages 2-12, what are the modifiers of outcome for different treatments or approaches?

KQ2a: Is the effectiveness of the therapies reviewed affected by the frequency, duration, and intensity of the intervention?

KQ2b: Is the effectiveness of the therapies reviewed affected by the training and/or experience of the individual providing the therapy?

KQ2c: What characteristics, if any, of the child modify the effectiveness of the therapies reviewed?

KQ2d: What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?

KQ3: Are there any identifiable changes early in the treatment phase that predict treatment outcomes?

KQ4: What is the evidence that effects measured at the end of the treatment phase predict long term functional outcomes?

KQ5: What is the evidence that specific intervention effects measured in the treatment context generalize to other contexts (e.g., people, places, materials)?

KQ6: What evidence supports specific components of treatment as driving outcomes, either within a single treatment or across treatments?

KQ7: What evidence supports the use of a specific treatment approach in children under the age of 2 who are at high risk of developing autism based upon behavioral, medical, or genetic risk factors?

PICOTS

Population. Children ages 2 – 12 who are diagnosed with an autism spectrum disorder (ASD) and children under age 2 at risk for diagnosis of an ASD

Interventions. Behavioral interventions, including variations of applied behavior analysis as well as developmentally-based models such as DIR/Floortime, among others; educational interventions, including the TEACCH program; allied health interventions, including occupational, physical, and speech therapy; medical interventions, including prescription and non-prescription treatments; and CAM approaches, including music therapy and nutritional therapies intended to modify the core symptoms of ASD

Comparators. No treatment, placebo, or comparative interventions from intervention list or combinations of interventions.

Outcomes and adverse events.

Primary outcomes.

- Changes in short-term targeted outcome areas, including social skills/interaction, language and communication, repetitive and other maladaptive behaviors, psychological distress, adaptive skills development and academic skills development

Secondary outcomes.

- Changes in long-term functional outcome areas, including adaptive independence/self care, academic/occupational engagement and attainment, psychological well-being, and interpersonal relationships/community involvement

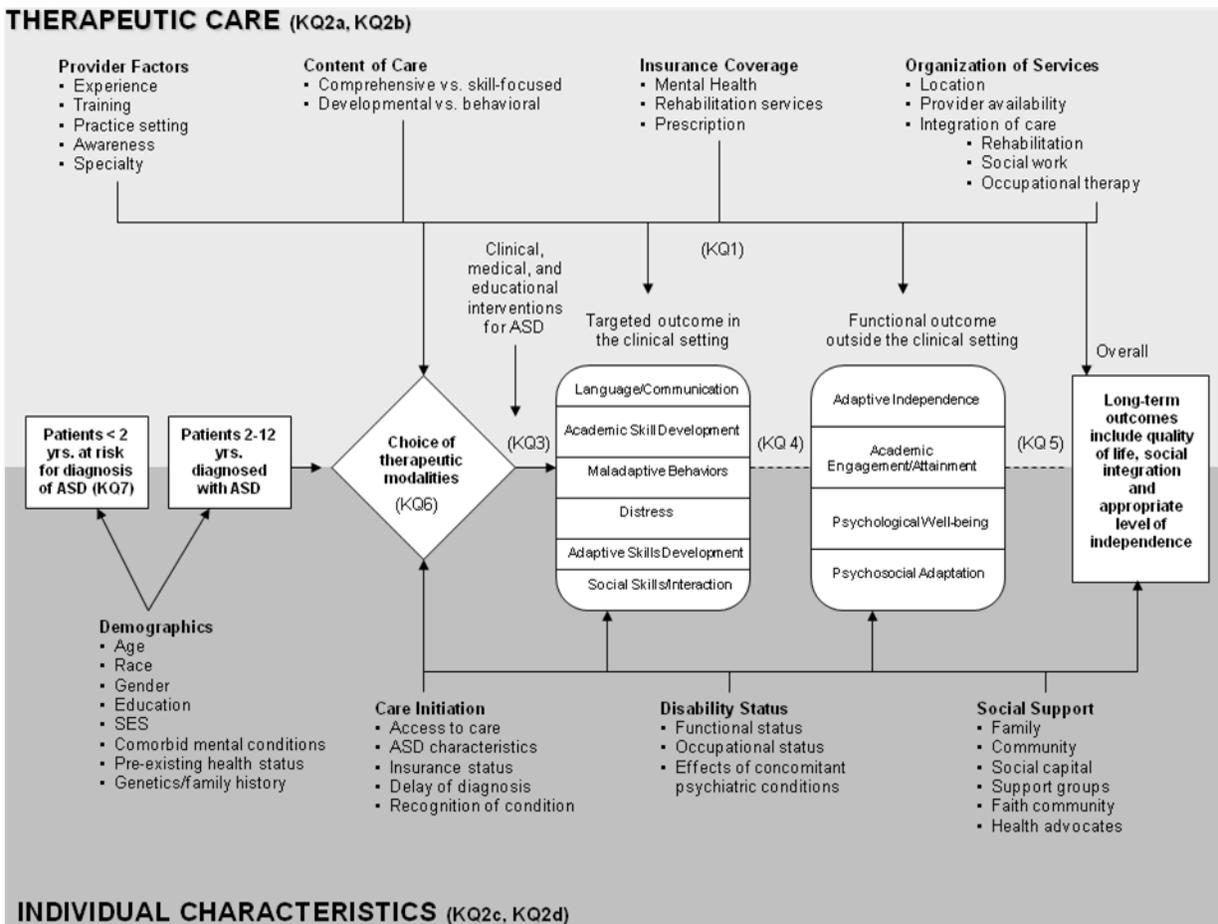
Adverse events.

- Adverse behavioral or psychosocial reactions to behavioral or other therapies (e.g. increased aggression or anxiety)
- Regression of language, skills, or behaviors
- Increases in/worsening of co-morbid symptoms
- Adverse reactions to drug therapies (e.g. somnolence, weight gain)
- Reduction in/negative influences on quality of life

Timing. We have defined the timing of outcomes to be studied as follows: short-term outcomes will be considered as those that occur ≤ 6 months and long-term outcomes as those that occur >6 months.

Setting. Settings will include medical, other clinical therapy settings, the home, and the educational setting.

III. Analytic Framework



IV. Methods

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

Table 1 lists preliminary inclusion/exclusion criteria developed based on our understanding of the literature developed during the topic refinement phase, input from content experts, and established principles of methodological quality. We reviewed these criteria during the first conference call with the TEP, including discussing varied study size cut points for specific interventions or study designs, particularly for behavioral studies. The TEP felt that criteria related to population, timeframe, setting, and language were appropriate. Based on TEP feedback, we will leave the admissible study size at 10 participants but will review the implications of that decision in terms of how many studies are excluded simply on size and in which categories of treatment they fall with the TEP in a follow-up call. We will revise the study size criteria, as appropriate, based on the input from the group at that time. The revisions will be subject to constraints of the existing scope of work (time and budget).

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Table 1: Inclusion/Exclusion Criteria

Category	Criteria
Study population	Children ages 2 – 12 who are diagnosed with an autism spectrum disorder (ASD) and children under age 2 at risk for diagnosis of an ASD
Study settings and geography	Developed nations/regions including the United States, Canada, United Kingdom, Western Europe, Japan, Australia, New Zealand, Israel, or South America
Time period	1980—present
Publication languages	English only
Admissible evidence (study design and other criteria)	<p><u>Admissible designs</u></p> <ul style="list-style-type: none"> Controlled trials, prospective trials with historical controls, prospective or retrospective cohort studies, and medium to large case series $N \geq 10$ <p><u>Other criteria</u></p> <ul style="list-style-type: none"> Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results Patient populations must include children ages 2-12 diagnosed with an ASD (Key Questions 1-6) or children ≤ 2 at risk for diagnosis (Key Question 7) Studies must address one or more of the following for ASDs: <ul style="list-style-type: none"> Treatment modality aimed at modifying the core symptoms of ASD Short- and long-term outcomes, harms, and quality of life related to treatment for core symptoms Relevant outcomes must be able to be abstracted from data presented in the papers Sample sizes must be appropriate for the study question addressed in the paper; single case reports or small case series (fewer than 10 subjects) will be excluded

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

Search the Literature. To ensure comprehensive retrieval of relevant research into therapies for children with autism spectrum disorder (ASD), our approach to the literature will include three key databases: the PubMed medical literature database, the PsycINFO psychology and psychiatry database, and the ERIC database of educational literature. Search strategies in each of

these databases will focus specifically on terms related to ASD, including keywords and subject terms, and a combination of subject terms and/or keywords representing therapeutic interventions (e.g., autism, asperger, pervasive development, therapeutics, etc.).

We will update the search semi-quarterly during the abstract and full-text review stages, adding relevant references to the pool of articles under consideration as needed. We will also update the search upon submission of the draft report and add relevant references as needed while the draft report is undergoing review. We will also incorporate references meeting our inclusion criteria or of particular relevance for background sections that may be brought forward by public/peer reviewers.

We will employ additional searches of the reference lists of existing systematic reviews or meta analyses of ASDs in children; the investigative team will also scan the reference lists of articles undergoing full text review for citations potentially meeting inclusion criteria.

Develop Data Collection Forms. We will develop data collection forms for abstract review, full text review and data abstraction. Abstract review forms will contain questions about primary exclusion/inclusion criteria. Full text review forms are somewhat more detailed and intended to assist in a) identifying studies that meet inclusion criteria and b) conducting an initial sort of studies into appropriate key questions. Finally, data abstraction forms will collect those data necessary for evidence tables and synthesis. Prior to data collection, we will develop and include *a priori* lists of effect modifiers (e.g., simultaneous therapies/synergistic effects, participants' developmental stage, setting of therapy, familial context, etc.) and expected outcomes for the data abstraction form. The form also will include an opportunity to report on funding source.

After reviewing a sample of relevant articles, the Methods and Content Leads will design the data collection forms and test them on multiple articles before initiating each stage of data abstraction. We expect that the data collection forms will undergo several revisions based upon these tests.

Initial Review of Abstracts. We will review all titles and abstracts identified through searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least 2 members of the investigative team. When differences between the reviewers arise, we will err on the side of inclusion. For studies without adequate information to make the determination, we will retrieve the full articles and review them against the inclusion/exclusion criteria.

C. Data Abstraction and Data Management

Retrieve and Review Articles. We will retrieve and review all articles meeting our predetermined inclusion/exclusion criteria or for which we have insufficient information to make a determination. The abstractor(s) and the co-Leads will reassess each retained article against the inclusion/exclusion criteria. For the studies meeting the second-round assessment, the abstractors will extract key data elements from the article(s) and enter them into evidence tables. The Methods Lead and content experts will review abstraction forms against the original articles for quality control. Differences between the abstractor and the reviewer will be resolved by consensus.

We will develop a simple categorization scheme for coding the reasons that articles, at the stage of full review, are not finally included in the report. The abstractor will note the reason for exclusion on the article cover page. We will then record that code in an EndNote® database, our

bibliography software, so that we can later compile a listing of excluded articles and the reasons for such exclusions.

Monitor study reviews. As reviews are conducted, the Project Coordinator and Administrative Support staff will track the status of each article. The Project Coordinator will maintain a master list of all the retrieved articles that indicates who was assigned the initial review and abstraction, its status in the review and abstraction process, the results of the review (e.g., whether it was selected for a full review or the reason why it was not, the date the initial review and abstraction was completed, the date it was reviewed and checked by the Methods Lead).

The Project Coordinator will also monitor the progress of reviews. Weekly during the review phase of the study, the Project Coordinator will report the number of abstracts and articles out for review to the Methods and Content Leads, contact reviewers to determine progress and collect completed reviews, and assess each evidence table entries for completeness. Twice a month, the project staff will meet to discuss the results and progress to date; review cases that have been particularly difficult to classify, abstract, interpret or adjudicate; and address any questions the review team may have. In addition, all abstractors and other project team members will routinely use email to communicate any concerns or questions arising during the course of the reviews.

A study characteristics spreadsheet will be developed by the Project Coordinator and Administrative Support staff to aid the Content Lead, Content Experts, Associate Director, and Investigators in compiling abstracted data. These spreadsheets will allow each author to count key data points, such as study location, study type, and number of study participants.

D. Assessment of Methodological Quality of Individual Studies

For this quality rating step, we expect to adapt either one of the types of grading schemes the Vanderbilt EPC has used to date or one of the approaches noted as “best practices” in the EPC’s review of systems to rate evidence. Two senior staff will separately assign quality grades; in our experience quality grading is conducted most efficiently and consistently by senior staff. We will record quality grades in the evidence tables.

E. Data Synthesis

Prepare evidence tables. We will enter data into evidence tables, using predetermined abbreviations and acronyms and otherwise attending to consistency across entries from the outset. The dimensions (i.e., areas of special focus, or the columns) of each evidence table will vary by key question, but the tables will contain some common elements, such as author, year of publication, study location (e.g., country, city, state) and time period, population description, sample size, and study type (e.g., randomized controlled trial, prospective observational study, etc).

F. Grading the Evidence for Each Key Question

Quality grading. We will also develop explicit criteria for rating the overall strength of the collective evidence on each key question into qualitative categories (e.g., good, fair, poor). In so doing, we will use established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending sample sizes), the quality of evidence (from the quality ratings on individual

articles), and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. We will make these judgments for each of the main key questions and any subquestions, if appropriate.

V. References

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8. Rogers SJ, Vismara LA. Evidence-based comprehensive treatments for early autism. *J Clin Child Adolesc Psychol* 2008;37:8-38.
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11. Blue Cross and Blue Shield Association Technology Evaluation Center. Special report: early intensive behavioral intervention based on applied behavior analysis among children with autism spectrum disorders. Available at: http://www.bcbs.com/blueresources/tec/vols/23/23_09.pdf. Accessed December 9, 2009.
12. Broadstock M, Doughty C, Eggleston M. Systematic review of the effectiveness of pharmacological treatments for adolescents and adults with autism spectrum disorder. *Autism* 2007;11:335-48.

VI. Definition of Terms – if applicable

N/A

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

12-09-09 Amendment II: Revision to inclusion/exclusion criteria for medical studies

Limiting medical studies included in the review to those including at least 30 participants with ASD and mean+SD age \leq 12.

Rationale: Most studies of medical interventions for ASD with fewer than 30 subjects report preliminary results that are replaced by later, larger studies. Therefore we will refine our inclusion criteria for medical studies to retain only those with at least 30 participants with ASD and mean+standard deviation age \leq 12 years, 11 months. This revision does not eliminate specific medical therapies from the review as treatments are typically assessed in larger studies following their preliminary investigation. In addition, seminal earlier literature on medical therapies will be addressed in our review of prior systematic reviews.

The project's AHRQ Task Order Officer approved this refinement on 12-09-09.

11-09-09 Amendment I: Revisions to inclusion/exclusion criteria

A. Limiting studies included in the review to those published from 2000 forward.

Rationale: In 2000, the DSM-IV-Text Revision revised the definition of Pervasive Developmental Disorder Not Otherwise Specified to correct an error that allowed this diagnosis to be ascribed when there was impairment in only one developmental area (i.e., social interaction, communication, or stereotyped behaviors, interests, or activities). The definition was clarified to require fundamental core social impairment in addition to either/both communication impairment or the presence of stereotyped behaviors, interests, or activities.

In addition to considerations of diagnostic shifts, parallel changes in available assessment methodologies and the introductions of 'gold-standards' of ASD assessment during this same time period also support such time delimited criteria in terms of refining our target population. Specifically, the commercial release of the Autism Diagnostic Observation System in 1999 and the revised version of the Autism Diagnostic Interview - Revised in 2003 allowed researchers to introduce metrics of sample comparison relative to core characteristics of ASD itself during this time period. As such, a review focusing on this decade of research will also be capable of speaking to the inclusion of such measurements and, when included, specific behavioral differences relative to core symptoms that may be impactful in thinking about the key elements

of interventions and therapies.

To ensure that seminal earlier literature is addressed by the current review, we will include a section assessing prior systematic reviews addressing therapies for ASD and published from 2008 forward. By reviewing those reviews systematically and summarizing them, we will capture key earlier literature without including it as primary data in our review.

B. Including studies with participants older than 12 years if the mean age plus standard deviation is \leq 12 years.

Rationale: Many studies include both children and adolescents, and few separate results in such a way that we can capture data separately on the participants younger than age 12. Our original inclusion criteria would require that we exclude studies of children that are not either exclusively in the 2 - 12 age range or that do not present data separately for that age range. While we are not searching for studies that are predominantly about adolescents, we do not want to lose those studies that are predominantly about children, but may include a small number of adolescents as well. We will therefore include studies in which the mean age + standard deviation of the participants does not exceed 12 years, 11 months.

C. Imposing no geographical limits on included studies

Rationale: We feel that the list of included countries on our current abstraction form is unnecessary as studies meeting all other inclusion criteria are likely able to inform treatment in the United States. We will eliminate this criterion.

The TEP for the project reviewed and approved these changes on 11-09-09.

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

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

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 (*Standard Language*)

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.