Evidence-based Practice Center Systematic Review Protocol

Project Title: Autism Spectrum Disorder—An Update

I. Background and Objectives for the Systematic Review

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder marked by impaired social communication and social interaction accompanied by atypical patterns of behavior and interest. As defined in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), ASD is differentiated from other developmental disorders by significant impairments in social interaction and communication, along with restrictive, repetitive, and stereotypical behaviors and activities.[1] Features of ASD can include a lack of reciprocal social interaction and joint attention (i.e., the ability to use nonverbal means such as pointing to direct others' attention to something in which the child is interested); marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, and gestures to regulate social interaction; restricted repetitive and stereotyped patterns of behavior, interests, and activities, such as apparently inflexible adherence to specific, nonfunctional routines or rituals, stereotyped and repetitive motor mannerisms; intense preoccupation with particular concepts or things; and atypical sensory processing.[2-4] Many children with ASD may also have impaired cognitive skills.[1,5]

Prevalence and burden of disease/illness. The prevalence of ASD in the United States is 11.3 cases per 1,000 (or 1 in 88) children living in the communities surveyed, with rate estimates varying widely by region of the country, sex, and race/ethnicity.[6] Considerably more males (1 in 54) than females (1 in 252) are affected. For some individuals, the core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may improve with intervention and maturation[7-9]; however, core deficits typically translate into varying developmental presentations that remain throughout the lifespan.[10] Longitudinal studies indicate that adults with ASD struggle to obtain traditional markers of adaptive independence.[11-15] The estimated costs of medical and nonmedical care (e.g., special education and daycare) for individuals with ASD are high. One study estimates that the total yearly societal per-capita cost of caring for and treating a person with autism in the United States is $3.2 million and about $35 billion for an entire birth cohort of individuals with autism.[16]

Etiology and risk factors. ASD has a strong genetic component, with heritability estimated to be as high as 90 percent in some studies.[17-19] A range of genes is implicated in susceptibility to ASD[19,20]; however, some evidence suggests that environmental exposures or context may also play a role in ASD development and neurogenetic expression.[21,22] Identification of specific genetic risk variants has proved to be challenging, and many researchers are now suggesting that there may be multiple pathways to this disorder, with prenatal and postnatal insult potentially contributing to presentation in some instances.[20] Current research[23,24] suggests that certain

metabolic and other maternal conditions (such as diabetes, hypertension, obesity, and influenza infection) during pregnancy may be associated with increased risk of ASD in offspring. Other studies have investigated the role of advanced maternal and paternal age,[25, 26] pesticide exposures,[27] and exposure to mercury and other heavy metals,[28] among other putative associations.

In addition to the genetic, parental, and environmental factors described above as potentially causative factors, being the sibling of another child diagnosed with ASD raises the risk of receiving an ASD diagnosis to 18.7 percent.[29] This risk varies by gender; 26.2 percent of younger male siblings and 9.1 percent of younger female siblings are at risk. This incidence increases twofold when two or more older siblings have ASD.

Interventions/treatment. The manifestation and severity of symptoms of ASD differs widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[30-34] that vary by a child's age and developmental status. The goals of treatment for ASD focus on improving core deficits in social communication and social interactions and on minimizing the impact of restricted behaviors, as changing these fundamental deficits may help children develop greater functional skills and independence.[3] Treatment frequently is complicated by symptoms or comorbidities that may warrant targeted intervention. There is no cure for ASD and no global consensus on which intervention is most effective.[33,35] Individual goals for treatment vary for different children and may include combinations of behavioral therapies, educational therapies, medical and related therapies, and allied health therapies; parents may also pursue complementary and alternative medicine (CAM) therapies.

Behavioral approaches are the cornerstone of treatment approaches for ASD. In 1987, Ivar Lovaas published findings[36] on a subgroup of children who demonstrated improvements in cognitive abilities and educational placement in response to intensive intervention based on the principles of applied behavior analysis (ABA). As a result, ASD was reconceptualized from a largely untreatable disorder[36] to a condition characterized by plasticity and heterogeneity, where there was hope for higher functioning and better outcomes for children receiving appropriate intervention. Subsequent research focused on social communication and behavioral impairments and used both highly structured approaches and natural/developmental approaches that deliver interventions within natural/everyday contexts (Floortime and the Social Communication Emotional Regulation Transactional Support model), some of which integrate approaches (Early Start Denver Model [ESDM]). These types of early and intensive treatment programs typically target behaviors and development more broadly, instead of focusing on a specific behavior of interest.[37] Positive effects seen with these approaches in terms of cognition and language have led to the suggestion that beginning intensive therapy at an earlier age may lead to greater improvements.[35,37,38] Recent systematic reviews and meta-analyses have highlighted the potential of early intervention to promote behavioral change.[31-34,38-47]

Pharmacologic agents used to treat ASD include antipsychotics, psychostimulants, and serotonin-reuptake inhibitors (SRIs), which generally are intended to treat common comorbidities of ASD rather than core symptoms. Only the atypical antipsychotics risperidone and aripiprazole have been approved by the U.S. Food and Drug Administration (FDA) to treat irritability in children 5 to 16 years of age with ASD.[48]

Other treatment approaches include educational interventions that are aimed primarily at older children, often target personal independence and social responsibility,[35] and focus both on traditional areas of academic progression/achievement and on addressing social, cognitive, and

behavioral issues in classrooms or through specialized instruction. Allied health approaches, such as speech- and language-focused modalities and sensory and auditory integration approaches, may target both core symptoms and associated deficits. CAM approaches are widely used despite little available evidence on efficacy, and include therapies such as acupuncture.[49-51]

Chronic management throughout different developmental periods is often required to maximize functional independence and quality of life by minimizing the core ASD features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families. Individual goals for treatment vary for different children and may include combinations of therapies. For many individuals core symptoms of ASD (impairments in communication and social interaction and restricted/repetitive behaviors and interests) may see improvements with intervention and over time[7-10]; however, deficits typically remain throughout the lifespan, although developmental expression may vary. There is no cure for ASD and currently no global consensus about which intervention strategies are most effective. Chronic management—often using multiple treatment approaches—may be required to maximize ultimate functional independence and quality of life by minimizing the core ASD features, facilitating development and learning, promoting socialization, reducing maladaptive behaviors, and educating and supporting families.

Objectives

The current systematic review will update a comprehensive review of therapies for children with ASD published in 2011.[34] The 2011 review assessed the literature reporting on any interventional approaches (i.e., behavioral, educational, medical, allied health, and CAM) and included more than 150 unique studies, the majority of which were considered of poor quality. Strength of the evidence for most interventions/outcomes was insufficient, with the exception of moderate and high ratings for the effectiveness and harms of the antipsychotics risperidone and aripiprazole. The strength of the evidence was considered low for the effectiveness of early intensive behavioral and developmental intervention. Positive outcomes from an early and intensive behavioral and developmental intervention were noted in cognitive performance, language skills, and adaptive behavior when the intervention was delivered over substantial intervals of time (i.e., 1–2 years). Variability in response to such approaches was tremendous, with subgroups of children who demonstrated a more moderated response. The ability to describe and predict these subgroups is limited.

Overall, the 2011 review found that medical interventions including risperidone and aripiprazole show benefit for reducing challenging behaviors in some children with ASD, but side effects are significant. Some behavioral and educational interventions that vary widely in terms of scope, target, and intensity have demonstrated effects, but the lack of consistent data limits understanding of whether these interventions are linked to specific clinically meaningful changes in functioning. Little evidence was available to assess allied health therapies or CAM. Information was similarly lacking on modifiers of effectiveness, generalization of effects outside the treatment context, components of multicomponent therapies that drive effectiveness, and predictors of treatment success.

Since the publication of the initial review in 2011, a sizable body of research has been published, particularly addressing behavioral interventions. Additional studies of behavioral interventions have the greatest potential to alter the low and insufficient strength of evidence

reported in the original review and potentially affect treatment recommendations. For this reason, our review will focus on behavioral studies.

In line with the 2011 review, we will define behavioral interventions as follows: behavioral interventions include early intensive behavioral and developmental interventions, social skills interventions, parent training, play/interaction-focused interventions, interventions targeting symptoms commonly associated with ASD such as anxiety, and other general behavioral approaches.

Early intensive behavioral and developmental interventions. We adopted a similar approach to the operationalization of the early intensive behavioral and developmental intervention category as Rogers and Vismara in their review of "comprehensive" evidence-based treatments for early ASD.[38] Interventions in this category all have their basis in or draw from principles of ABA, with differences in methods and setting. ABA is an umbrella term describing principles and techniques used to assess, treat, and prevent challenging behaviors and the promotion of new, desired behaviors. The goal of ABA is to teach new skills, promote generalization of these skills, and reduce challenging behaviors with systematic reinforcement. The principles and techniques of ABA existed for decades before being specifically applied to the study and treatment of ASD.

We include in this category two intensive interventions that have published manuals to facilitate replication: the University of California, Los Angeles (UCLA)/Lovaas model and the Early Start Denver Model (ESDM). These two interventions have several key differences in their theoretical frameworks and in how they are implemented, although they share substantial similarity in the frequent use of high-intensity (many hours per week, one-on-one) instruction using ABA techniques. They are described together here because of these similarities. We note, however, that the UCLA/Lovaas method relies heavily on one-on-one therapy sessions during which a trained therapist uses discrete trial teaching with a child to practice target skills, while ESDM blends ABA principles with developmental and relationship-based approaches for young children.

The other treatment approaches in this category also incorporate ABA principles and may be intensive in nature; often, however, they have not been documented in a manual. We have classified these approaches broadly as UCLA/Lovaas based given their similarity in approach to the Lovaas model. A third particular set of interventions included in this category are those using principles of ABA to focus on key pivotal or foundational skills and behaviors (such as motivation to communicate or initiation of communication), rather than global improvements. These approaches often emphasize parent training as a modality for treatment delivery (e.g., Pivotal Response Training, Hanen More than Words, social pragmatic intervention, etc.) and may focus on specific behaviors such as initiating or organizing activity or on core social communication skills. Because they emphasize early training of parents of young children, they will be reviewed in this category.

Social skills interventions. Social skills interventions focus on facilitating social interactions and may include peer training and social stories.

Play/interaction-focused interventions. These approaches use interactions between children and parents or researchers to affect outcomes such as imitation or joint attention skills or the ability of the child to engage in symbolic play.

Interventions focused on behaviors commonly associated with ASD. These approaches attempt to ameliorate symptoms such as anger or anxiety, often present in children with ASD, using techniques such as Cognitive Behavioral Therapy (CBT) and parent training focused on challenging behaviors.

Additional behavioral interventions. We will categorize approaches not cleanly fitting into the behavioral categories above in this group.

We will include a list of studies of all approaches (medical, allied health, etc.) meeting the review criteria as an appendix to the updated report.

II. The Key Questions

We have modified the Key Questions (KQs) from the 2011 review to focus on behavioral interventions. KQ 1 focuses on outcomes of interventions. KQ 2 addresses how the characteristics of the child/family or the intervention may modify outcomes. Such data could be used to target treatments appropriately. KQs 3 and 4 seek to identify whether changes measured during or after an intervention predict outcomes. KQ 5 assesses the generalizability of intervention effects, and KQ 6 identifies the "active ingredients" in a given intervention. We identified little literature addressing KQs 3–6 in the 2011 review and anticipate that they will remain largely unanswered in the update; however, we will seek to identify data addressing them. KQ 7 addresses treatments for very young children considered to be at risk for ASD, based upon behavioral, medical, or genetic risk factors.

Question 1

Among children ages 0–12 years who have ASD, what are the short- and long-term effects of available behavioral treatment approaches? Specifically:

a. What are the effects on core symptoms (e.g., social deficits, communication deficits, and repetitive behaviors) in the short term (≤6 months)?
b. What are the effects on commonly associated symptoms (e.g., motor, sensory, medical, mood/anxiety, irritability, and hyperactivity) in the short term (≤6 months)?
c. What are the longer term effects (>6 months) on core symptoms (e.g., social deficits, communication deficits, and repetitive behaviors)?
d. What are the longer term effects (>6 months) on commonly associated symptoms (e.g., motor, sensory, medical, mood/anxiety, irritability, and hyperactivity)?

Question 2

Among children ages 0–12 years, what are the modifiers of outcome for different treatments or approaches?

a. Is the effectiveness of the therapies reviewed affected by the frequency, duration, and intensity of the intervention?

b. Is the effectiveness of the therapies reviewed affected by the training and/or experience of the individual providing the therapy?
c. What characteristics, if any, of the child modify the effectiveness of the therapies reviewed?
d. What characteristics, if any, of the family modify the effectiveness of the therapies reviewed?

Question 3

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

Question 4

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

Question 5

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

Question 6

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

Question 7

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

Table 1 outlines the PICOTS (**p**opulation, **i**ntervention, **c**omparators, **o**utcomes, **t**iming, and **s**etting) for each KQ.

Table 1. PICOTS characteristics

| Question	Population	Intervention	Comparator(s)	Outcomes	Timing	Setting
KQs 1–6	Children with ASD ages 0 months to 12 years	Behavioral approaches aimed at modifying ASD symptoms	Placebo, other intervention, or no intervention	• ASD symptom severity • Language/communication • Academic skill development • Maladaptive behaviors • Distress • Adaptive skills • Social skills/interaction • Adaptive independence • Academic engagement/ attainment • Psychological well-being • Psychosocial adaptation • Quality of life • Social integration • Appropriate level of independence • Harms	Short term ≤ 6 months Long term > 6 months	Any setting (clinic, home, school, etc.)
K Q7	Children ages 0–2 years considered to be at risk for ASD because of sibling status or lacking a confirmed diagnosis but considered highly suspicious for ASD due to develop-mental and behavioral vulnerab-ilities	Behavioral approaches aimed at modifying ASD symptoms	Placebo, other intervention, or no intervention	• ASD symptom severity / diagnostic outcome • Language/communication • Cognitive skills • Motor skills • Maladaptive behaviors • Distress • Adaptive skills • Social skills/interaction • Adaptive independence • Harms	Short term ≤ 6 months Long term > 6 months	Any setting (clinic, home, school, etc.)

ASD = autism spectrum disorder; KQ = key question; PICOTS = Population, Intervention, Comparators, Outcomes, Timing, Setting

III. Analytic Framework

Figure 1 illustrates the analytic framework for the 2011 review and the current update. The figure summarizes the process by which families of children with ASD make and modify treatment choices. Circled numbers indicate the KQs, and their placement indicates the points in the treatment process where they are likely to arise. This update focuses on behavioral interventions for children with ASD or considered to be at risk for ASD. The population of interest is patients 0–12 years diagnosed with ASD. Individuals engage in interventions, which may lead to specific outcomes (KQ 1). Outcomes may be modified by characteristics of the child/family or of the intervention (KQ 2). KQ 3 involves identifiable changes early in the

treatment process that may affect outcomes. KQ 4 involves the relationship between targeted outcomes in the treatment setting and functional outcomes outside the treatment setting. KQ 5 involves generalization of interventions to other contexts, and KQ 6 addresses components of treatments that may drive outcomes, the "active ingredients" of treatments. KQ 7 addresses treatments for very young children considered to be at risk for ASD. Target outcomes in the treatment setting include ASD symptom severity, language/ communication, academic skill development, maladaptive behaviors, distress, adaptive skills development, and social skills/interaction. Functional outcomes outside the treatment setting include adaptive independence, academic engagement/attainment, psychological well-being, and psychosocial adaptation; for children considered to be at risk, the outcomes include changes in ASD symptom severity or diagnostic outcome, motor skills, and cognitive skills. Long-term outcomes include quality of life, social integration, and appropriate level of independence. Harms of intervention are also considered.

Figure1. Analytic framework
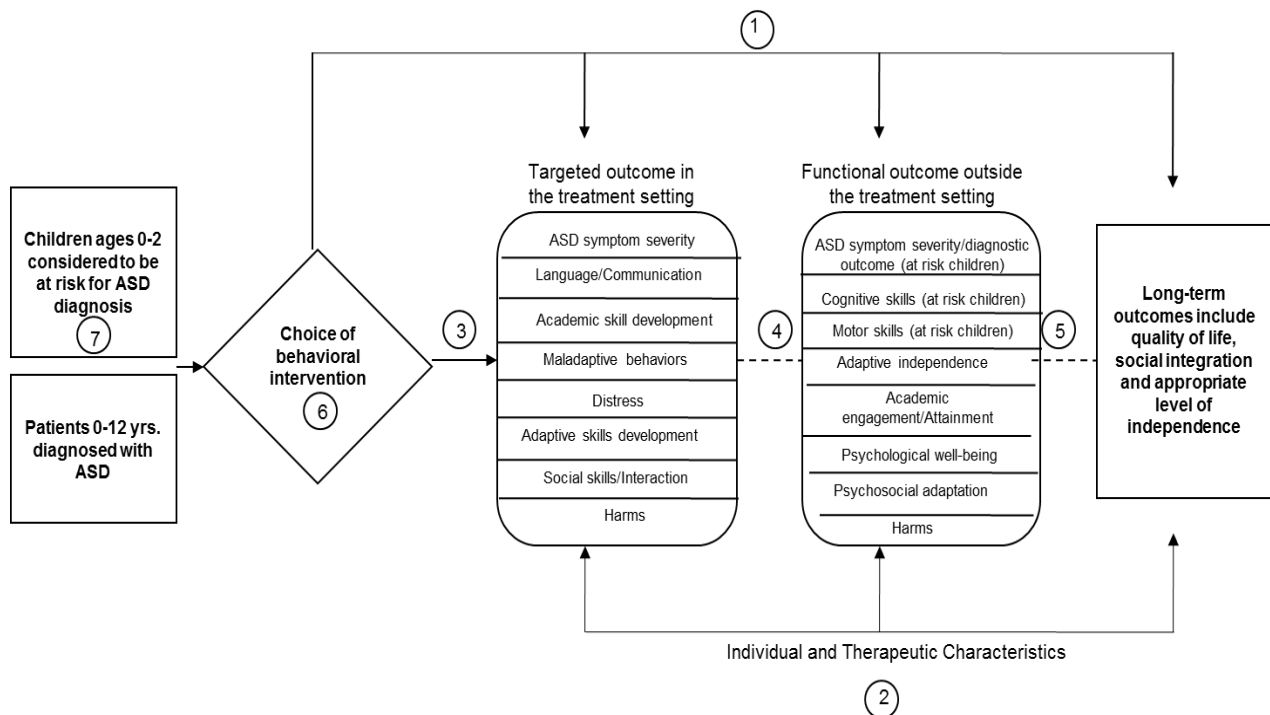
ASD = autism spectrum disorder

IV. Methods

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

Table 2 outlines inclusion criteria for this update. As noted, we will adhere to the parameters set forth in the original 2011 review but with the exception of limiting eligible studies to behavioral studies that include comparison groups. We will exclude case series, as additional case series (studies without a comparison group) are unlikely to lead to a change in the strength

of evidence (SOE). The currently established SOE (based on the 2011 report) will only shift with the addition of comparative studies of high quality.

We will also limit eligible studies to those written in the English language, as our content experts, key informants, and technical experts involved with the 2011 review agreed that significant research in the area is generally published in English.

Table 2. Inclusion criteria

Category	Criteria
Study population	Children ages 0-12 with ASD or 0-2 considered to be at risk for ASD based on sibling status or early developmental/behavioral vulnerabilities highly suspicious of ASD
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs RCTs, prospective and retrospective cohort studies, and nonrandomized controlled trials Other criteria Original research studies providing sufficient detail regarding methods and results to enable use and aggregation of the data and results Studies must have relevant population & ≥ 10 participants with ASD Studies must address one or more of the following for ASD: -Treatment modality -Predictors of treatment outcomes -Generalization of treatment outcomes to other contexts -Drivers of treatment outcomes Relevant outcomes must be able to be abstracted from data in the papers Data must be presented in the aggregate (vs. individual participant data)

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

Databases. To ensure comprehensive retrieval of relevant studies of therapies for children with ASD, we will use three key databases: the MEDLINE® medical literature database via the PubMed® interface, the PsycINFO® psychology and psychiatry database, and the Education Resources Information Center database (ERIC[SM]). These databases, plus the Cumulative Index of Nursing and Allied Health Literature (CINAHL®) were also searched for the original review. We tested the unique contributions of CINAHL for the current update; however, the database did not yield any unique citations, a finding in line with recent assessments of the overall utility of the CINAHL database.[52] Thus, we will not include the CINAHL database in the update review. Search strategies for each of these databases will focus specifically on terms related to ASD and treatment or transitional issues, including keywords, subject headings, and a combination of subject headings and/or keywords (e.g., autism, ASD, therapy, therapeutics, etc.). We will search for studies published from 2010 to the present to account for any delays in indexing of the literature published since the 2011 review.

Search updates. During our reviews of abstracts and full-text articles, we will update the literature search quarterly by adding relevant studies as needed. We will also update the search when the draft report is submitted and will add relevant studies as needed while the draft report is undergoing peer review. We will also incorporate studies that meet our inclusion criteria or are relevant as background material that may be identified by both public and peer reviewers.

Hand searching. We will carry out hand searches of the reference lists of recent systematic reviews or meta-analyses of therapies for ASD; the investigative team will also scan the

reference lists of articles that are included after the full-text review phase for studies that potentially could meet our inclusion criteria.

Grey literature. As we will not be reviewing medications or devices, we will not request Scientific Information Packets or regulatory information.

C. Data Abstraction and Data Management

Data-extraction forms. We will refine the data-collection forms for the abstract review, the full-text review, and data extraction that were used in the 2011 review. The forms used for the abstract review will contain questions about the primary exclusion and inclusion criteria. The forms used for the full-text review are more detailed and are intended to assist in (a) identifying studies that meet inclusion criteria and (b) initially sorting the studies according to the KQs. Finally, data-extraction forms will collect those data necessary to create evidence tables and perform data synthesis. We anticipate that these data will include those related to baseline participant characteristics (age, diagnosis, symptom severity, etc.), intervention characteristics (description, fidelity/adherence, etc.), and outcomes.

Before data collection, we will develop lists of potential confounders and effect modifiers (e.g., age, IQ, simultaneous therapies/synergistic effects, comorbidities/coexisting conditions, sociocultural context, etc.), including those reported in the 2011 review, and expected outcomes for the data-extraction form that will be informed by our clinical expertise. The form also will include a field in which to report the funding source of a study.

After reviewing a sample of relevant articles, the team will assess the data-collection forms from the 2011 review and test them on multiple articles before beginning each stage of data extraction. We expect that the data-collection forms will undergo revisions as these tests are completed.

Initial review of abstracts. We will review all the titles and abstracts identified through our searches against our inclusion/exclusion criteria. Each abstract will be reviewed by at least two 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-text articles and review them against the inclusion/exclusion criteria.

Retrieving and reviewing articles. We will retrieve and review all articles that meet our predetermined inclusion criteria or for which we have insufficient information to make a decision about eligibility. Each article will be reviewed by at least two members of the investigative team. Differences between the reviewers will be adjudicated by a third party.

Deciding which outcomes are to be extracted. We will extract data on the following key outcomes, as based on our clinical expertise and experience with the 2011 review, our initial scan of the literature, and our abstract review: cognitive outcomes, adaptive behavior outcomes, core ASD symptom changes, language outcomes, and challenging/disruptive behavior outcomes. Prespecifying each individual measure to extract is not feasible, given the large number of assessment tools/measures used in the ASD literature; however, we anticipate that we will focus on well-established, validated outcome measures or techniques that incorporate measures of agreement (e.g., measures to assess consensus of coding of communicative acts, etc.).

For studies that meet the conditions of the second-round assessment, the extractors will extract key data and study-quality elements from the article(s) and enter them into evidence tables. We anticipate that these elements will include population and intervention characteristics such as age, diagnoses, intervention approach, and dosage; assessment characteristics including instruments used and fidelity measures employed; and outcomes reported. A second reviewer will review those data-extraction forms against the original articles for quality control. Differences in data coding 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(s) for exclusion on the article abstraction form. We will then record those codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database so that we can later compile a listing of excluded articles and the reasons for such exclusions.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the overall quality of each included study by using the quality-assessment approach developed in our prior review on therapies for children with ASD and informed by the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[53] This quality-assessment approach considered factors related to study design, diagnostic approach, participant ascertainment, intervention characteristics, outcomes measurement, and statistical approach and included questions such as: Did the authors report differences in or hold steady all concomitant interventions? Were outcomes coded and assessed by individuals blinded to the intervention status of the participants? And for randomized controlled trials, was there an intent-to-treat analysis?

Two senior investigators will independently assess each included study with disagreements between assessors resolved through discussion to reach consensus.

E. Data Synthesis

Preparing evidence tables. We will enter data into evidence tables by using predetermined abbreviations and acronyms consistently across all entries. The dimensions (i.e., areas of special focus, or the columns) of each evidence table may vary by KQ as appropriate, 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.).

Synthesizing results. Given significant differences in populations, interventions, and outcomes measured in the ASD literature, we anticipate a largely qualitative synthesis of findings. However, we will work with our statistician to determine whether a quantitative analysis can be performed. For example, we may be able to provide inference on subgroups via Bayesian mixed-effects meta-regression. This allows for the borrowing of strength across studies, where appropriate, using random effects to account for the variation in effects among similar (but nonidentical) studies.

Presentation of results. Within each KQ, we will organize results by type of intervention, which mirrors the organization of the 2011 review. Within each category, we will present results by study design, with a focus on those designs less subject to bias (i.e., randomized controlled trials, controlled trials) and those studies rated as of higher quality in our quality-assessment process.

F. Grading the Strength of Evidence for Individual Comparisons and Outcomes

Assessing the strength of evidence. We will utilize explicit criteria for rating the overall strength of the collective evidence for the key outcomes identified above for each KQ into qualitative categories (e.g., low, moderate, high, insufficient). 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 as appropriate for each of the KQs.

The SOE evaluation will be that stipulated in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews,*[53] which emphasizes the following five major domains: risk of bias (low, medium, high), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct, indirect), precision (precise, imprecise), and reporting bias (suspected, undetected). Two senior staff will independently grade the body of evidence; disagreements will be resolved as needed through discussion or third-party adjudication. We will record SOE assessments in tables, summarizing for each key outcome. We will assess the SOE only for those studies rated as good or fair in quality (low or moderate risk of bias).

Determining the overall strength-of-evidence rating. We will use the same approach we used to determine SOE that we used in the 2011 review: We required at least three fair-quality studies to be available to assign a low SOE rather than considering it to be insufficient. For determining the SOE for effectiveness outcomes, we only assessed the body of literature deriving from studies that included comparison groups. We required at least one good-quality study for moderate SOE and two good-quality studies for high SOE. In addition, to be considered "moderate" or higher, intervention-outcome pairs needed a positive response on two of the domains other than risk of bias. Once we had established the maximum SOE possible based upon these criteria, we assessed the number of studies and the range of study designs for a given intervention-outcome pair and downgraded the rating when the cumulative evidence was not sufficient to justify the higher rating. When no studies are available for an outcome or comparison of interest, we will grade the evidence as insufficient.

G. Assessing Applicability

We will assess the applicability of findings reported in the included literature to the general population of children with ASD by determining the PICOS (**p**opulation, **i**ntervention, **c**omparator, **o**utcomes, and **s**etting) in each study and developing an overview of these elements for each intervention category. We will also review potential modifiers of effect of treatment to

identify subgroups, which may include different age groups, severity of ASD, or level of education. We anticipate variation in the scope of services offered across the country and in the populations and outcomes in each study given the heterogeneity of ASD.

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VI. Definition of Terms

Not applicable.

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. Changes made to the protocol should not be incorporated throughout the various sections of the protocol. Instead, protocol amendments should only be noted in section VII of the protocol, preferably in a tabular format (please see the example below), and the date of the amendment noted at the top of the protocol. A sample table is shown below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in the protocol.	Specify where the change would be found in the protocol.	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use a justification such as "because the AE/TOO/TEP/Peer reviewer told us to," but rather explain what the change hopes to accomplish.

VIII. Review of Key Questions

For all Evidence-based Practice Center (EPC) reviews, Key Questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, the Key Questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end-users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy 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. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer Reviewers do not participate in writing or editing of the final report or other products. 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 Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the Evidence Report. Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. 290-2012-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.