Evidence-based Practice Center Systematic Review Protocol

Project Title: Medical and Sensory-Related Therapies for Children with Autism Spectrum Disorder—An Update

Initial publication date: Comparative Effectiveness Review (CER) # 26 was originally released in April, 2011. The first surveillance (assessment for need for update) was completed in January, 2012 and found a "low" need to update the CER. The second assessment was completed in October, 2012 and found a "medium" need to update sections of the CER. The 2014 review, Therapies for Children With Autism Spectrum Disorder: Behavioral Interventions Update, targeted behavioral interventions.

I. Background and Objectives for the Systematic Review

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder broadly defined by impaired social communication as well as restricted or repetitive patterns of behavior and interest. As defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM-5), specific features of ASD include deficits in social and emotional reciprocity (e.g., atypical social approaches, conversational impairment, atypical sharing of interests, attention, and affect); deficits in nonverbal communication (e.g., poorly integrated verbal and nonverbal communication, atypical body-language and gesture use, deficits in use and understanding of nonverbal communication), and deficits in maintaining appropriate relationships (e.g., challenges with peer interest, vulnerabilities forming friendships, difficulties adjusting behavior to suit social contexts) as well as restricted and repetitive patterns of behavior such as stereotyped speech, motor movements, or use of objects; excessive adherence to routine or insistence on sameness; intense interest patterns; and atypical sensory interests or responses. Symptoms of the disorder impair and limit everyday functioning and are thought to be evident in early childhood; although they may not be fully evident until later ages. Although not a core symptom, many children with ASD may also have significant cognitive impairment.

The prevalence of ASD in the United States is 14.7 cases per 1,000 children living in the communities surveyed, or 1 in 68, with rate estimates varying widely by region of the country, sex, and race/ethnicity.[1] Considerably more males (1 in 42) than females (1 in 189) are affected. For some individuals, symptoms of ASD may improve with intervention and maturation; however, core deficits typically translate into varying developmental presentations that persist throughout the lifespan.[2] Longitudinal studies indicate that adults with ASD struggle to attain traditional markers of adaptive independence.[3-7]

The estimated costs of medical and non-medical care (e.g., special education and daycare) for individuals with ASD are high, with costs in the billions for an entire birth

cohort[8] and an estimated additional cost of $17,000 per year to care for a child with ASD compared with a child without ASD.[9] A study of healthcare utilization in a large group health plan revealed increased medication costs in older children with ASD compared with younger children with ASD, as well as similarly aged adolescents without an ASD; other care costs were also higher in this population, including a significantly increased rate of hospitalizations.[10]

Children who enter into specialized intervention services at young ages can demonstrate substantial gains in cognitive and adaptive functioning.[11-16] Early diagnosis has also been shown to improve family functioning and reduce associated service system demands in the short-term, with potential impact across the lifespan when linked to appropriate and effective intervention.[17] It is hypothesized that early intervention may ultimately reduce the considerable lifetime cost and system demands associated with providing care and support to individuals with ASD and their families.[8, 18-22]

The manifestation and severity of symptoms of ASD differ widely, and treatments include a range of behavioral, psychosocial, educational, medical, and complementary approaches[23-27] that vary by a child's age and developmental status. The goals of treatment for ASD typically focus on improving core deficits in communication, social interactions, or restricted behaviors, as changing these fundamental deficits may help children develop greater functional skills and independence.[28] 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.[29, 30] Individual goals for treatment vary for different children and may include combinations of behavioral therapies, educational therapies, medical and related therapies, approaches targeting sensory issues, and allied health therapies; parents may also pursue complementary and alternative medicine (CAM) therapies.

Table A-1 in the appendix outlines medical treatments reported in recent ASD literature. The antipsychotics risperidone (Risperdal) and aripiprazole (Abilify) have been specifically approved by the U.S. Food and Drug Administration (FDA) for treatment of irritability and challenging behaviors in ASD (Table A-1). Many other medications are used off –label to manage behavioral symptoms such as anxiety and hyperactivity. In addition, devices such as hyperbaric oxygen chambers may be used to treat symptoms of ASD, though hyperbaric oxygen has not been approved by the FDA for ASD treatment.[31] Sensory-focused treatments vary and target dysfunctional sensory processing through approaches such as environmental modification, sensory or auditory integration therapy, or weighted vests.[27, 32, 33]

Rationale for an updated review

A scan of the literature published since an AHRQ review of treatments for children with ASD (2011),[15] an updated review of behavioral interventions (2014),[34] and input from technical experts suggested that data are adequate to warrant a review update.

In consultation with clinical experts and stakeholders, and based on our preliminary scan of the literature, we determined that focusing the review update on medical approaches and approaches to address sensory challenges reflect both areas of clinical relevance and

sufficient newly published literature for a review update. We identified additional potential areas of focus for a review update (i.e., parent-delivered behavioral interventions and interventions to address severe challenging behavior); we will continue to monitor the literature in these areas in future surveillance phases and may address them in future review updates.

As noted, the current review update will focus on interventions addressing sensory challenges and medical therapies, including combination medical/behavioral therapies. We will conduct an update of the evidence for these types of interventions available since the publication of the two prior AHRQ reviews.[15, 34] We anticipate that the current review update will be published as two separate reviews—one addressing medical approaches and one addressing approaches targeting sensory challenges.

II. The Key Questions

The Key Questions evolved from the team discussions, expert input, and reviewer comments during the topic surveillance. The Key Questions reflect the unmet need for a relevant synthesis of evidence from comparative studies on the relative benefits of medical interventions and interventions addressing sensory challenges to manage ASD symptoms in children. Key Questions reflect the questions addressed in the 2011 review,[46] with the exception of targeting medical and sensory approaches specifically. We also eliminated a question on approaches for children at risk for ASD as such children are unlikely to be included in studies in the target areas for this review update.

We define medical interventions broadly as interventions involving the administration of external substances to the body or use of external, non-behavioral procedures to treat symptoms of ASD, which includes pharmacologic agents, diet therapies, vitamins and supplements, chelating agents, electroconvulsive therapy, transcranial magnetic stimulation and hyperbaric oxygen, among other modalities.

We define allied health interventions targeting sensory challenges in line with the DSM-5 definition and definitions used in other reviews of sensory-focused interventions.[35, 36] DSM-5 classifies sensory challenges as a manifestation of the core symptom of restricted and repetitive patterns of behavior, interests, or activities. The DSM describes sensory challenges as "hyper- or hyporeactivity to sensory input, manifested through extreme responses to specific sounds or textures, excessive smelling or touching of objects, fascination with lights or spinning objects, and sometimes apparent indifference to pain, heat, or cold." [37] Interventions targeting sensory challenges are typically described as designed to provide controlled sensory experiences in order to encourage the modulation and integration of information from the environment, thus promoting adaptive responses to sensory inputs. Though the field lacks consensus on a definition of sensory-focused approaches, interventions typically use sensory modalities to target behaviors that may be associated with sensory-related impairments.[36, 38]

We will consider clinic-based or adult-directed approaches, conducted in either clinic-based or naturalistic settings, that use sensory experiences to ameliorate sensory challenges or impairments and have a primary basis in theories of sensory processing or

motor skills as "interventions targeting sensory challenges." These types of interventions include sensory and auditory integration, brushing, massage, weighted vests or blankets, therapeutic swings, and sensory-focused environmental modification. We will not include studies of other approaches (e.g., educational interventions) that may address a sensory-related outcome in the current review.

Key Questions (KQ)

KQ1: Among children ages 2-12 with ASD, what is the comparative effectiveness (benefits and harms) of medical treatments?

a) What are the effects on core symptoms (e.g., deficits in social communication and interaction; restricted, repetitive patterns of behavior, interests, or activities including hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment) in the short term (≤6 months)?

b) What are the effects on commonly associated symptoms (e.g., motor, 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, medical, mood/anxiety, irritability, and hyperactivity)?

KQ2: Among children ages 2-12 with ASD, what is the comparative effectiveness (benefits and harms) of interventions targeting sensory challenges?

a) What are the effects on core symptoms (e.g., deficits in social communication and interaction; restricted, repetitive patterns of behavior, interests, or activities including hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of the environment) in the short term (≤6 months)?

b) What are the effects on commonly associated symptoms (e.g., motor, 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, medical, mood/anxiety, irritability, and hyperactivity)?

KQ3: Among children ages 2-12 with ASD, what are the modifiers of outcome for different (a) medical treatments or (b) interventions targeting sensory challenges?

a) Is the effectiveness of the therapies reviewed affected by the frequency, duration, intensity, or dose of the intervention?

b) Is the effectiveness of the therapies reviewed affected by co-interventions or prior treatment or the training and/or experience of the individual providing the therapy?

c) What characteristics (e.g., age, symptom severity), 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?

KQ4: What is the time to effect of medical interventions or interventions targeting sensory challenges?

KQ5: What is the evidence that effects measured at the end of the treatment phase predict long-term functional outcomes of medical interventions or interventions targeting sensory challenges?

KQ6: Is the effectiveness of medical interventions or interventions maintained across environments or contexts (e.g., people, places, materials)?

KQ7: What evidence supports specific components of treatment with medical interventions or interventions targeting sensory challenges as driving outcomes, either within a single treatment or across treatments?

Public Comments and Changes to Posted Key Questions

The draft Key Questions (KQ) were posted for public comments (11/18/15 – 12/08/15). Five individuals or organizations commented on the questions. These comments necessitated minor changes to the KQ, review scope, and inclusion criteria.

Specifically, comments noted a need to clarify that the focus of all KQ is exclusively on medical and sensory-related interventions and to define both areas (medical, interventions addressing sensory challenges) clearly. Comments also discussed a need to stratify results by age group (e.g., 2-6 years, 7-12 years) and to clarify that sensory issues are considered core symptoms of ASD. One comment also noted that modifying characteristics (KQ3) should be clearly defined.

We modified the KQ to remove sensory symptoms from among the commonly associated symptoms listed in KQ1b, 1d, 2b, and 2d. We also clarified that KQs 4-7 address medical and sensory-related interventions exclusively. We will not pre-specify modifying characteristics of interest (e.g., age, symptom severity) as, in the opinion of our content experts and the technical experts who helped to inform this review, multiple modifiers may be assessed and little consensus exists on key modifying variables beyond age and symptom severity. We will, therefore, report what is reported in each study.

We will stratify our presentation of results by age groups where possible. We anticipate grouping interventions more discretely into categories such as antipsychotics, stimulants, vitamin supplements, and therapeutic diets for medical interventions and categories such as processing/integration, environmental/compensatory, activity-based, coaching, and massage/touch/feeling for sensory interventions.

Population, Intervention, Comparator, Timing and Setting (PICOTS)

Population

The population for this review update is children with ASD between the ages of 2 and 12 years.

Interventions

Medical Treatments

We will define this category broadly as interventions involving the administration of external substances to the body or use of external, non-behavioral procedures to treat symptoms of ASD, which includes pharmacologic agents, diet therapies, vitamins and supplements, chelating agents, electroconvulsive therapy, transcranial magnetic stimulation and hyperbaric oxygen, among other modalities.

Interventions to Target Sensory Challenges

As noted, we define sensory challenges in line with the broad description used by the DSM 5. We will consider clinic-based or adult-directed approaches, conducted in clinic-based or naturalistic settings, that use sensory experiences to ameliorate sensory challenges or impairments and have a primary basis in theories of sensory processing or motor skills as "interventions targeting sensory challenges." These types of interventions include sensory and auditory integration, brushing, massage, weighted vests or blankets, therapeutic swings, and sensory-focused environmental modification**.**

We will not include primarily behavioral interventions or educational interventions, though we note that these interventions may have sensory components.

Comparators

Comparators include no treatment, wait list control, placebo, or other interventions.

Outcomes

We will address the following broad outcome categories. These outcomes are child-specific but are also reflective of family/community functioning. We note that we will address both sensory-specific and broader outcomes of interventions targeting sensory challenges.

Intermediate outcomes

- ASD symptom severity
- Expressive or receptive language/communication
- Academic skill development
- Maladaptive behaviors
- Distress

- Adaptive skills development
- Social skills/interaction
- Harms of interventions

Final health outcomes

- Symptom severity or diagnostic outcome
- Functional communication
- Cognitive skills
- Motor skills
- Adaptive independence
- Academic engagement/attainment (e.g., mainstream school placement or integration)
- Social participation
- Psychosocial well-being
- Psychosocial adaptation
- Harms of interventions

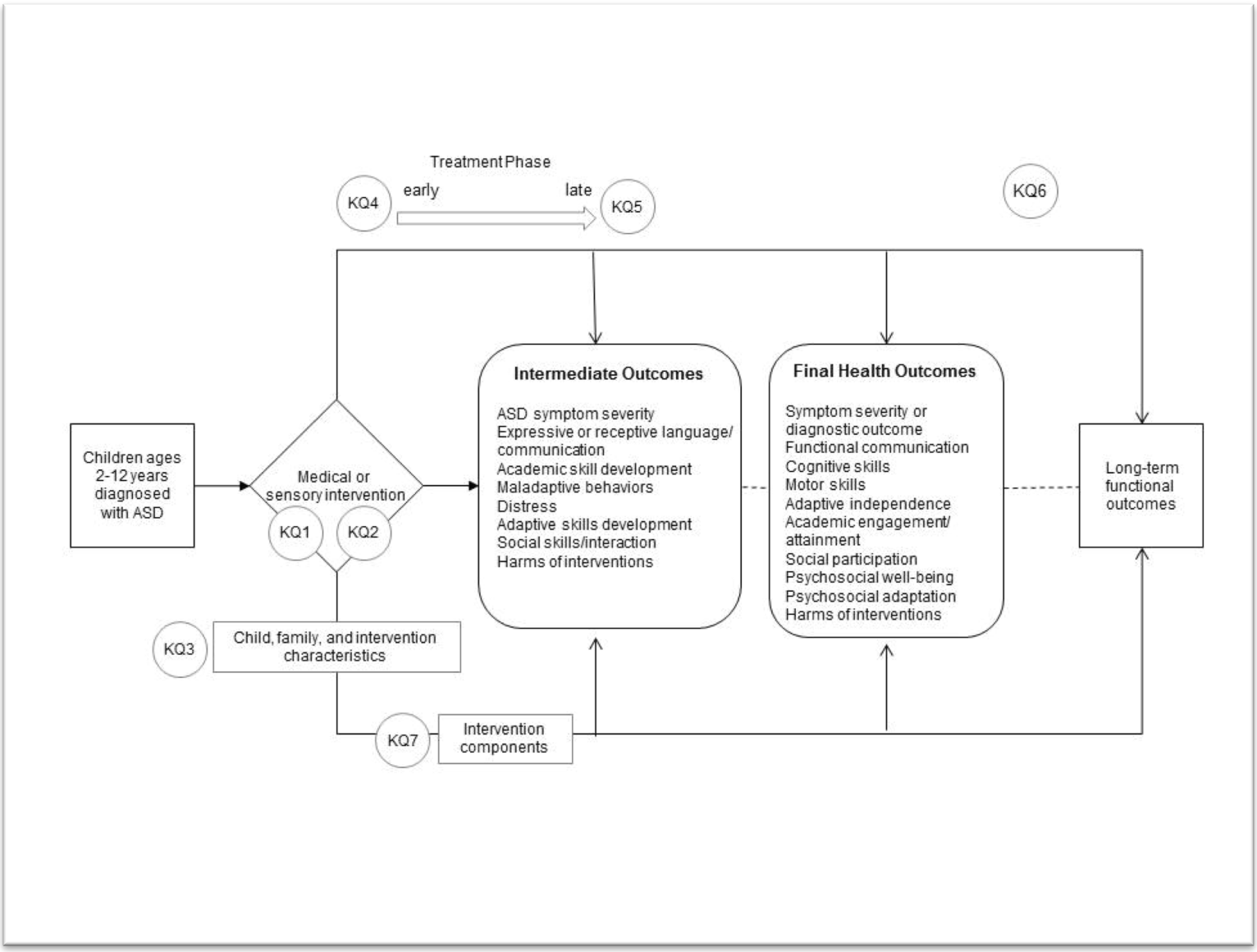
Timing and Setting

We will include studies of any length or follow-up and in any setting (clinic, home, school, etc.). We define short-term outcomes as those measured ≤ 6 months post-treatment and long-term outcomes as those measured >6 months post-treatment.

III. Analytic Framework

The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guide the literature search and synthesis.

Figure 1. Analytic framework



IV. Methods

The methods for this systematic review will follow the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[39] and the PRISMA-P[40] statement checklist for reporting. We have registered the protocol in PROSPERO (CRD42016033941).[41]

Inclusion and Exclusion of Studies in the Review

Table 1 outlines inclusion criteria. We note an increasing number of randomized and comparative studies in individuals with ASD. The size and quality of literature supports

limiting inclusion to comparative studies and excluding data from non-comparative study reports (e.g., case reports or case series). Eligible RCTs must have a total minimum sample size of 10. We will require a higher minimum sample size (n=20) for other comparative studies as they typically have fewer controls for bias than RCTs.

We recognize that these study design criteria will exclude single-subject or single-case experimental designs that have been used to study interventions targeting sensory challenges. These studies are challenging to incorporate in a meaningful way in comparative effectiveness reviews, which attempt to evaluate the effectiveness of interventions at the population level. To mitigate the exclusion of such studies; however, we will include summaries of recent high quality (as assessed using the ROBIS [42] tool) reviews that have included such studies and will discuss our findings in light of those in other reviews.

We will include studies published in English only. In the opinion of our content experts, much of the relevant literature on ASD is published in English; however, we will scan a sample of non-English abstracts to gauge the number of anticipated non-English studies that would meet inclusion criteria. If we identify a significant number, we will include an appendix table outlining the PICOTS represented in the abstracts. We will search for studies published from 2010 to the present to capture literature since the previous searches for the 2011 review and 2014 review update.

We will use a best evidence approach to determine final inclusion of studies (i.e., if evidence from randomized studies is insufficient to address a KQ or specific outcomes, we will consider evidence from observational literature as well as factors related to the relevance of studies to determine if the inclusion of additional studies is warranted).[43]

Eligible studies must also report one or more outcomes of interest and include children at least 2 years of age and up to and including age 12. Studies must include only children with a diagnosis of ASD. We will require that studies including mixed age (children and adolescents or adults) populations either report data separately by age group or include children with a mean age plus standard deviation of 2 years to 12 years 11 months.

Table 1. Inclusion criteria

Category	Criteria
Study population	Children ages 2-12 with ASD (mean age plus standard deviation is ≤ 12 years and 11 months)
Publication languages	English only
Admissible evidence (study design and other criteria)	**Admissible designs** Randomized controlled trials, prospective and retrospective cohort studies with comparison groups, and nonrandomized controlled trials **Other criteria** Original research studies published from 2010—present and not addressed in prior reviews Studies must have relevant population and ≥20 participants with ASD (non-RCTs) or at least 10 total participants (RCTs) Studies must address one or more of the following for ASD:

Category	Criteria
	-Outcomes of interest -Treatment modality of interest -Predictors or drivers of treatment outcomes (e.g., biomarkers, clinical changes) -Maintenance of outcomes across environments or contexts -Sufficiently detailed methods and results to enable data extraction -Reporting of outcome data by target population or intervention

Searching for the Evidence

Published literature

To identify the available published literature, we will search MEDLINE via PubMed, EMBASE, the Cochrane Library, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PsycINFO®. We will use the search strategies presented in Tables A-2 and A-3 of the Appendix, modified as needed for each specific database.

We will use a date limit of 2010 to the present for the search of indexed literature.

Grey literature

We will search web sites of organizations likely to conduct research, issue guidance, or generate policies for ASD (Table A-4 in the Appendix) to inform the review's background and discussion sections. We will search government and regulatory agency web sites for contextual information on benefits and harms of ASD interventions. We will search ClinicalTrials.gov for information about relevant ongoing trials and to confirm that we have obtained available publications of results from completed trials.

Hand searching

We will scan the reference lists from recent relevant systematic reviews and papers that meet the screening criteria for the review. We will reference those lists against our database of retrieved records and look for citations not included in our database that may be eligible for inclusion.

Scientific Information Packets (SIPs)

The Scientific Resource Center (SRC) will notify relevant stakeholders (including device manufacturers and pharmaceutical companies) about the opportunity to submit Scientific Information Packets (SIPs). We will compare the information in the SIPs with the biomedical literature and grey literature retrieval. We will extract information from the SIPs that is not already captured by published study results or other sources. We will apply the same inclusion and exclusion criteria relevant to Key Questions to studies identified via SIPs.

Literature updates

We will conduct literature search updates periodically during preparation of the review and will conduct a final literature search update at the time of peer review of the draft report. We will screen and include relevant studies with each update. We will also incorporate relevant, eligible studies identified by peer reviewers or public commenters in the final report.

Selecting Studies

Screening forms

We will develop forms for screening and preliminary data extraction. The forms will include questions to determine study eligibility based on the exclusion and inclusion criteria. The forms will include additional questions to describe study characteristics and assist in grouping of the eligible studies by Key Question. We will use DistillerSR™ for screening studies.

Retrieving and reviewing articles

We will use dual review and two levels of screening to identify eligible studies and assign exclusion codes for ineligible records. We will review the titles and abstracts from the retrieved records against the pre-defined inclusion/exclusion criteria. We will exclude records that are deemed ineligible by two independent reviewers from the investigative team. Records marked as eligible or unclear (e.g., insufficient information to make a decision about eligibility) by one or both reviewers will be promoted for a second screening at the full text level.

We will obtain the full text article for each record that was not excluded at the abstract screening level. Two members of the investigative team will independently review the full text paper of retained records for inclusion in the review. Screening decision disagreements will be adjudicated via team discussion or by a senior investigator/methodologist. We will use the same screening forms and inclusion/exclusion criteria to assess eligibility of citations recommended by peer and public reviewers and for the literature retrieved by updated literature searches. We may contact study authors for additional data or clarification if needed.

Data Management

We will develop a coding scheme to document the reasons for exclusion. We will record exclusion codes in an EndNote® (Thomson Reuters, New York, NY) bibliographic database. We will list excluded records and reasons for exclusion in the report. We will create data extraction forms to collect detailed information on the study characteristics, intervention(s), comparator(s), arm details, reported outcomes and outcome measures, and risk of bias assessment. We will deposit data used in a meta-analysis into the Systematic Review Data Repository (SRDR).

Data Extraction

To ensure quality and consistent data extraction, we will pilot the data extraction forms. Two team members will independently extract study characteristics and outcomes from a subset of studies into Excel or other files suitable for uploading into the Systematic Review Data Repository (SRDR). The team will review and compare the data extraction tables and make recommendations to revise the form if needed.

We will use dual independent extraction for studies that meet the eligibility criteria. We will identify and link related publications and studies to avoid duplicate extraction of outcome data. We will extract study and design characteristics (e.g., study design, year,

setting, funding source, study arms); patient characteristics (e.g., age, symptom severity, treatment history); diagnostic and/or assessment methods; intervention characteristics (e.g., description, components, frequency, duration, intensity); outcomes reported (e.g., core symptoms, associated symptoms, harms); and length of followup. We will extract additional information, when reported, to assess whether the effectiveness of interventions differs by potential modifying characteristics including intervention delivery (e.g., duration, setting, training/experience of provider); intervention co-treatment or prior treatment; patient characteristics; or family characteristics.

We will use consistent and precise terminology for reporting study characteristics and interventions. We will define and categorize the outcomes to the degree that the literature includes operational definitions. We will check sources other than published literature (e.g., FDA, clinical trial data from device manufacturers or pharmaceutical companies via SIPs) for additional information on harms.[44]

Assessment of Methodological Risk of Bias

We will evaluate the overall methodologic risk of bias of individual studies using the ASD-specific assessment approach developed and used in our prior reviews of interventions for ASD and informed by the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[39] This risk of bias approach considers factors related to study design, diagnostic approach, participant ascertainment, intervention characteristics, outcomes measurement, and statistical approach and includes 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? For randomized controlled trials, was there an intent-to-treat analysis?

We will use the ROBIS tool[42] to assess the quality of recent, relevant systematic reviews addressing medical interventions or interventions targeting sensory challenges.

Two senior investigators will assess each included study independently. Disagreements will be resolved through discussion or by an independent senior investigator/methodologist. We will use the thresholds we establish in prior reviews to assess overall high, medium or low risk of bias.

We will assess the risk of bias based upon the study-defined primary outcome(s). We may assess the risk of bias for additional outcomes if assessors determine that the risk of bias for an outcome of interest is likely to differ from the overall study risk of bias assessment.

Synthesizing Results

We will provide a qualitative and quantitative synthesis of studies meeting our review criteria. We will summarize data related to core and associated symptoms with estimates of treatment effects and confidence intervals when possible. We will omit high risk of bias studies from analyses but will conduct sensitivity analyses to gauge their effects. We

will provide summary level information about the high risk of bias studies in appendix tables.

We will describe outcomes across similar studies by Key Question and intervention. We will quantify study-level heterogeneity via random effects, which we prefer to the use of an arbitrary variance cutoff value or statistical tests for heterogeneity (e.g., Q statistics, I^2 scores). The decision about pooling a set of studies using random effects will depend on whether the studies can be considered exchangeable from a population of studies of the same phenomenon. This should be determined based on the design and quality of the studies, independent of the studies' relative effect sizes, rather than on the degree of statistical heterogeneity.

Many ASD studies contain few patients, limiting the ability of a study to overcome differences in baseline characteristics and variability of outcome reporting. Some differences among study populations may be accounted for in the model by adjusting for factors such as age, symptom severity, or comorbidities in the study sample. Newer approaches to random effects meta-analysis allow for robust (e.g., non-parametric) estimates of variation that do not rely on the assumption of normally distributed random effects. This permits us to account for "outlier" studies in the meta-analytic model without either discarding them unnecessarily or allowing them to influence meta-estimates disproportionately.

Analysis of effectiveness among subgroups will be done formally, within a statistical model via indicator variables or by stratifying results and organizing the report in such a way that end users are provided with overall outcomes data and information specific to subgroups defined by factors such as age and symptom severity that can be easily identified and stand alone as needed.

Subgroup analysis may be used to evaluate the intervention trajectory in a defined subset of the participants in a trial, or in complementary subsets. Subgroup analysis can be undertaken in a variety of ways, from completely separate models at one extreme, to simply including a subgroup covariate in a single model at the other, with multilevel and random effects models somewhere in the middle. Generally, trial sizes are too small for sub-group analyses within individual studies to have adequate statistical power.

Meta-regression models describe associations between the summary effects and study-level data; that is, it describes only between-study and not between-patient variation. We will use multilevel models, which boost the power of the analysis by sharing strengths across subgroups for variables where it makes sense to do so, or subgroup analysis (with random effects meta-analysis) to explore heterogeneity if there are a sufficient number of studies.

Grading the Strength of Evidence

We will use explicit criteria for rating the overall strength of the evidence for intervention-final outcome pairs for which the overall risk of bias is not high. 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 assess strength of evidence as stipulated in the Effective Health Care Program's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* updated strength of evidence guide.[45] Current guidance on strength of evidence evaluation emphasizes the following major domains: study limitations (low, medium, high level of limitation), consistency (inconsistency not present, inconsistency present, unknown, or not applicable), directness (direct, indirect), precision (precise, imprecise), and reporting bias (present, undetected). Intervention-outcomes pairs will be given an overall evidence grade based on the ratings for the individual domains.

The assessment of the study limitations domain will be derived from the risk of bias of the individual studies that addressed the Key Question and specific outcome under consideration. The domains of consistency and precision will be assessed based on the direction and variation of the estimates. We will assess reporting bias of randomized controlled trials by examining outcomes of trials as reported in resources such as ClinicalTrials.gov to determine if prespecified outcomes are not reported in the published literature. We assign an overall grade (high, moderate, low or insufficient) for the strength of evidence for each key outcome (Table 2).

Table 2. Strength of evidence grades and definitions

Grade	Definition
High	Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. Findings are stable, i.e., another study would not change the conclusions.
Moderate	Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. Findings are likely to be stable, but some doubt remains.
Low	Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	No evidence or unable to estimate an effect. No confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding a conclusion.

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 strength of evidence assessments in tables, summarizing results for each outcome. When no studies are available for an outcome or comparison of interest, we will grade the evidence as insufficient.

We will determine outcomes of greatest clinical importance for assessing strength of the evidence in consultation with the TEP and our content experts.

Determining Strength of Evidence (SOE)

We will use the same approach we used to determine SOE that we used in the 2011 and 2014 reviews: We required at least three moderate risk of bias studies to be available to assign a low SOE rather than considering it to be insufficient.[15, 34] 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 low risk of bias study for moderate SOE and two low risk of bias studies for high SOE. In addition, to be considered "moderate" or higher, intervention-outcome pairs needed a positive response on two of the SOE domains (other than study limitations). 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.[15, 34]

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 population, intervention, comparator, and setting in each study and developing an overview of these elements for each intervention category.

We anticipate that areas in which applicability will be especially important to describe will include child-related factors such as age, symptom severity or diagnosis, baseline language and IQ/cognitive skills, and baseline adaptive behavior; parent-related factors including education; and intervention-related factors including provider training and dosage/intensity of intervention.

V. References

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VI. Definition of Terms

- **Medical interventions:** interventions involving the administration of external substances to the body or use of external, non-behavioral procedures to treat symptoms of ASD, which includes pharmacologic agents, diet therapies, vitamins and supplements, chelating agents, electroconvulsive therapy, transcranial magnetic stimulation and hyperbaric oxygen, among other modalities.

- **Interventions targeting sensory challenges:** clinic-based or adult-directed approaches that use sensory experiences to ameliorate sensory challenges or impairments and have a primary basis in theories of sensory processing or motor skills. These types of interventions include sensory and auditory integration, brushing, massage, weighted vests or blankets, therapeutic swings, and sensory-focused environmental modification.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

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 healthcare 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 constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and 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 do they contribute to the writing of the report. They 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 TOO 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. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three 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. 290201500003l 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.

Appendix

Table A-1. Medications Addressed in Recent RCTs Including Children with ASD

Drug	Company
Anticonvulsants	
Carbamazepine (Tegretol®)	Novartis Pharmaceuticals Corporation, East Hanover, NJ
Riluzole	Apotex Research Private Ltd., Bangalore, India
Valproate/ Valproic acid	Catalent Pharma Solutions, St. Petersburg, FL
First-generation antipsychotics	
Haloperidol	Sandoz Inc., Princeton, NJ
Second-generation (atypical) antipsychotics	
Aripiprazole (Abilify®)	Otsuka America Pharmaceutical Inc., Tokyo, Japan
Olanzapine (Zyprexa®)	Eli Lilly and Company, Indianapolis, IN
Olanzapine/Fluoxetine (Symbyax®)	Eli Lilly and Company, Indianapolis, IN
Quetiapine (Seroquel®)	AstraZeneca Pharmaceuticals LP, Wilmington, DE
Risperidone (Risperdal®)	Janssen Pharmaceuticals Inc., Titusville, NJ
Ziprasidone	Pfizer Roerig, New York, NY
Central nervous system (CNS) stimulants	
Methylphenidate (Ritalin®)	Watson Pharma Inc., Corona, CA
Other (mood stabilizer, diuretic, NSAID, antihypertensive, non-SSRI antidepressant)	
Atomoxetine (Strattera®)	Eli Lilly and Company, Indianapolis, IN
Bumetanide	Eon Labs, Inc., New Hyde Park, NY
Celecoxib (Celebrex®)	G.D. Searle LLC Division of Pfizer Inc., Skokie, IL
Donepezil (Aricept®)	Eisai Inc., Tokyo, Japan
Hyperbaric oxygen (HBOT) chambers	Perry Baromedical, Reimers Systems, Sands Chambers, Sechrist Products
Lofexidine (BritLofex®)	Britannia Pharmaceuticals Ltd., England, UK
Mecamylamine (Vecamyl®)	Nexgen Pharma, Inc., Irvine, CA
Selective serotonin reuptake inhibitors (SSRI)	
Fluvoxamine	Mylan Pharmaceuticals Inc., Morgantown, WV
Alpha-agonists	
Clonidine	Teva Pharmaceuticals Inc., Sellersville, PA

Table A-2. PubMed Search Strategy: ASD Interventions

	Search	Records
1	"Child Development Disorders, Pervasive"[Mesh]	22400
2	(autistic[tiab] OR autism[tiab] OR asperger[tiab] OR asperger's[tiab] OR aspergers[tiab] OR pervasive development[tiab] OR pervasive developmental[tiab] OR pdd[tiab]) NOT medline[sb]	5401
3	#1 OR #2	27801
4	therapy[sh] OR therapeutics[mh] OR teaching[mh] OR psychotherapy[mh] OR treatment outcome[mh]	7275093
5	(treatment[tiab] OR therapy[tiab] OR intervention[tiab] OR “control group”[tiab] OR randomized[tiab] OR outcome[tiab] OR randomized[tiab] OR efficacy[tiab] OR effectiveness[tiab] OR comparison[tiab] OR compared[tiab] OR trial[tiab] OR “pilot study”[tiab]) NOT medline[sb]	780487
6	#4 OR #5	8048106
7	#3 AND #6	9790

8	(newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR review[pt] OR practice guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR meta-analysis[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt])	5440529
9	#7 NOT #8	6654
10	#9 limited to ("2010/01/01"[Date - Publication] : "3000"[Date - Publication])	3770

Notes: Retained n=3768 after duplicates discarded

Table A-3. PubMed Search Strategy: ASD Medical Interventions

Search		Records
1	"Child Development Disorders, Pervasive"[Mesh]	22400
2	(autistic[tiab] OR autism[tiab] OR asperger[tiab] OR asperger's[tiab] OR aspergers[tiab] OR pervasive development[tiab] OR pervasive developmental[tiab] OR pdd[tiab]) NOT medline[sb]	5401
3	#1 OR #2	27801
4	("Drug Therapy"[Mesh]) OR ("drug therapy" [Subheading] OR "Medication Therapy Management"[Mesh])	2368930
5	("drug therapy"[tiab] OR medication[tiab] OR placebo[tiab] OR pharmacologic[tiab] OR psychopharmacology[tiab] OR psychotropic[tiab] NOT medline[sb])	37368
6	#4 OR #5	2406272
7	#3 AND #6	1919
8	(newspaper article[pt] OR letter[pt] OR comment[pt] OR case reports[pt] OR review[pt] OR practice guideline[pt] OR news[pt] OR editorial[pt] OR historical article[pt] OR meta-analysis[pt] OR legal cases[pt] OR published erratum[pt] OR congresses[pt])	5440529
9	#7 NOT #8	1007
10	#9 limited to ("2010/01/01"[Date - Publication] : "3000"[Date - Publication])	433

Notes: Retained n=28 after duplicates discarded

Table A-4. Key organization/agency web sites to be included in grey literature search

Organization/Agency	Site URL
American Academy of Child and Adolescent Psychiatry	http://www.aacap.org/
American Academy of Pediatrics	www.aap.org/en-us/
American Psychiatric Association	www.psychiatry.org
Autism Society	www.autism-society.org/
Autism Speaks	www.autismspeaks.org
Health Resources and Services Administration: Maternal and Child Health	mchb.hrsa.gov/programs/autism/index.html
National Autism Association	www.nationalautismassociation.org/
National Institute of Child Health and Human Development	www.nichd.nih.gov
National Institute of Mental Health	www.nimh.nih.gov
National Institute of Neurological Disorders and Stroke	www.ninds.nih.gov
ResearchAutism	http://researchautism.net/

Sensory Integration Global Network	http://www.siglobalnetwork.org/
US Autism and Asperger Association	www.usautism.org
US Centers for Disease Control and Prevention: ASD	www.cdc.gov/ncbddd/autism/index.html
US Department of Health and Human Services: Interagency Autism Coordinating Committee	iacc.hhs.gov