Effective Health Care Program

Future Research Needs Paper
Number 9

Future Research Needs for Attention Deficit Hyperactivity Disorder:

Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Future Research Needs

Number 9

Future Research Needs for Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers, Long-Term Effectiveness in All Ages, and Variability in Prevalence, Diagnosis, and Treatment

Version 2

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10056-I

Prepared by:
RTI-UNC Evidence-based Practice Center
Research Triangle Park, NC

Investigators
Bradley N. Gaynes, M.D., M.P.H.
Robert Christian, M.D.
Lissette Saavedra, Ph.D.
Roberta Wines, M.P.H.
Dan Jonas, M.D., M.P.H.
Meera Viswanathan, Ph.D.
Alan Ellis, M.S.
Carol Woodell, B.S.P.H.
Tim Carey, M.D., M.P.H.

AHRQ Publication No. 12-EHC008-EF
May 2012

This report is based on research conducted by the RTI-UNC Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290 2007 10056 I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care researchers and funders of research make well-informed decisions in designing and funding research and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of scientific judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical research and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances.

This report may be used, in whole or in part, as the basis for research design or funding opportunity announcements. AHRQ or the U.S. Department of Health and Human Services endorsement of such derivative products or actions may not be stated or implied.

None of the investigators has any affiliation or financial involvement that conflicts with the material presented in this report.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact: EffectiveHealthCare@ahrq.hhs.gov.

Suggested citation: Gaynes BN, Christian R, Saavedra L, Wines R, Jonas D, Viswanathan M, Ellis A, Woodell C, Carey T. Future Research Needs for Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers, Long-Term Effectiveness in All Ages, and Variability in Prevalence, Diagnosis, and Treatment. Future Research Needs No. 9 (Prepared by RTI-UNC Evidence-based Practice Center under Contract No. 290-2007-10056-I.) Rockville, MD: Agency for Healthcare Research and Quality, May 2012. AHRQ Publication No. 12-EHC008-EF. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm

Addendum, March 15, 2012: This report was posted for public comment from January 18, 2012 to February 14, 2012. Minor revisions were made on pages 30 and 31 to emphasize the importance of generalizability and the potential effect of socioeconomic status to modify the effectiveness of treatments on outcome and note that the draft comparative effectiveness review was the basis for this future research needs report.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

As part of a new effort in 2010, AHRQ has supported EPCs to work with various stakeholders, including patients, to further develop and prioritize the future research needed by decisionmakers. The Future Research Needs products are intended to inform and support researchers and those who fund research to ultimately enhance the body of comparative effectiveness evidence so that it is useful for decisionmakers.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. CERs will be updated regularly.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Sonia Tyutyulkova
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

The RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (RTI–UNC EPC) would like to thank our stakeholder panel who gave generously of their time. Their expertise and enthusiasm helped drive this project. We would also like to thank our friends and colleagues, Lynda Booker, Alice Charach, Mary Gauld, and Pat Carson at the McMaster University EPC, authors of the 2010 draft AHRQ report. Thanks also to Mattias Johnson and Shannon Brode, from the University of North Carolina at Chapel Hill Cecil G. Sheps Center for Health Services Research, for their work in developing our online surveys; Christiane Voisin, also from the Sheps Center, for library support; and our Task Order Officer, Sonia Tyutyulkova, for support and guidance. We also express our gratitude to RTI staff Loraine Monroe, Judy Cannada, and Susan Beck, Publications Specialists, and Laura Small, Editor.

Contributors

Ann Abramowitz, Ph.D.
Emory University
Atlanta, GA

Anne Chelminski, M.D., M.P.H.
University of North Carolina
Chapel Hill, NC

Lisa Clements, Ph.D.
Missouri HealthNet
Missouri Department of Social Services
Jefferson City, MO

Tammy Davis, Ed.D.
American School Counselor Association
Alexandria, VA

Tiffany Farchione, M.D.
U.S. Food and Drug Administration
Division of Psychiatry Products
Silver Spring, MD

Stephen Faraone, M.D.
SUNY Upstate Medical University
Syracuse, NY

Laurence Greenhill, M.D.
New York State Psychiatric Institute
New York, NY

Penelope Knapp, M.D.
UC Davis M.I.N.D. Institute
Sacramento, CA

Sarah Mulligan, M.Ed.
Division for Early Childhood (DEC),
Council for Exceptional Children
Missoula, MT

Sue Visser, Ph.D.
Centers for Disease Control and Prevention
National Center for Birth Defects and
Developmental Disabilities
Atlanta, GA

Benedetto Vitiello, M.D.
National Institutes of Health
National Institute of Mental Health
Rockville, MD

Julie Zito, Ph.D.
University of Maryland, Baltimore
Baltimore, MD

Contents

Tables

Figures

Appendixes

Executive Summary

Background

This Future Research Needs (FRN) report is based on a draft Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review, "Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment."

The Key Questions (KQs) were:

- KQ 1: Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?
- KQ 2: Among people ages 6 years or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of followup or treatment, including, but not limited to, 12 months or more of continuous treatment?
- KQ 3: How do (a) underlying prevalence of ADHD, and (b) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics?

Findings in the draft review for KQ 1 supported the use of parent behavior training in preschoolers both for oppositional behaviors and for ADHD symptoms, with no adverse events reported. For preschoolers, psychostimulant medications are also generally safe and efficacious for improving behavior and can provide benefits in addition to parent training. However, adverse events, especially irritability and moodiness, can lead to discontinuation, and use for several months to a year slightly affects growth rate.

For KQ 2, long-term effectiveness and safety studies of several psychostimulants in children over the age of 6 years and adolescents found they are efficacious for control of inattention and overactivity for extended periods of time. Few serious adverse events were noted. Publications from the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (MTA) study provide the best data for long-term outcomes. By 3 years, no single intervention group showed superior benefit, which is likely because of individuals obtaining a complex range of interventions in the community.

The findings for KQ 3 included results from a systematic review and meta-regression that estimated the prevalence of ADHD among those ages 18 or younger at 5.29 percent, with more boys than girls identified and the highest rates of disorder occurring in 5- to 10-year-olds. Primary sources of variability were identified as methodological rather than geographic. Fewer studies are available that document prevalence in adult, adolescent, or preschool age groups.

In the draft review there was little or no evidence to draw conclusions for several questions. We developed the list of evidence gaps in Table A based on information from the draft review and input from the stakeholder panel. We developed an analytic framework to show the relationships between the evidence gaps, populations, interventions, comparators, outcomes, timeframes, and settings (PICOTS), and Key Questions (Figure A).

Table A. Preliminary evidence gaps by Key Question

Evidence Gap	Relevant Key Question
For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions.	KQ 1
For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs alone compared with pharmacological treatments, alone or in combination with psychosocial treatments.	KQ 1
Among children less than 6 years of age with disruptive behavior disorder or ADHD, there is a paucity of research examining positive child treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based interventions, or other cross-sector evaluations), alone or in combination with pharmacological interventions, and effects on specific subgroups.	KQ 1
For preschoolers with disruptive behavior disorder or ADHD, there are few efficacy and effectiveness studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components based on the child's needs.	KQ 1
Among people less than 6 years of age with disruptive behavior disorder or ADHD, there is a lack of high-quality studies on efficacy and effectiveness of biofeedback and working memory training.	KQ 1
Among children ages less than 6 years with disruptive behavior disorder or ADHD, there is a paucity of studies documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions.	KQ 1
For children less than 6 years of age with ADHD, limited data are available on the influence of parental preferences regarding treatment approaches or modes of service delivery on short- and long-term outcomes.	KQ 1
Among children less than 6 years of age with disruptive behavior disorder or ADHD, there is a paucity of studies that disassemble the key components of available psychosocial treatment programs (e.g., specific parent training techniques compared to treatment components targeting the child and variants in service delivery to accommodate parental preferences).	KQ 1
Conflicting results from treatment studies of children less than 6 years of age with disruptive behavior disorder or ADHD show improvements in ADHD symptoms when the parent behavior training protocol is flexible and when the protocol is not flexible. Among children less than 6 years of age with disruptive behavior disorder or ADHD, studies comparing the relative efficacy of flexible versus nonflexible parent behavior training protocols are currently not available.	KQ 1
Limited data are available from studies with appropriate comparison groups about long-term outcomes for preschool interventions.	KQ 1
Among children less than 6 years of age with ADHD, there is a paucity of prospective studies that compare the efficacy, effectiveness, and harms of single and/or combination pharmacotherapies with other single or combined pharmacotherapies (e.g., stimulants vs. nonstimulants).*	KQ 1
For children ages 6 years or older with ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions.	KQ 2
For children ages 6 years or older with ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs alone compared with pharmacological treatments, alone or in combination with psychosocial treatments.	KQ 2

Table A. Preliminary evidence gaps by Key Question (continued)

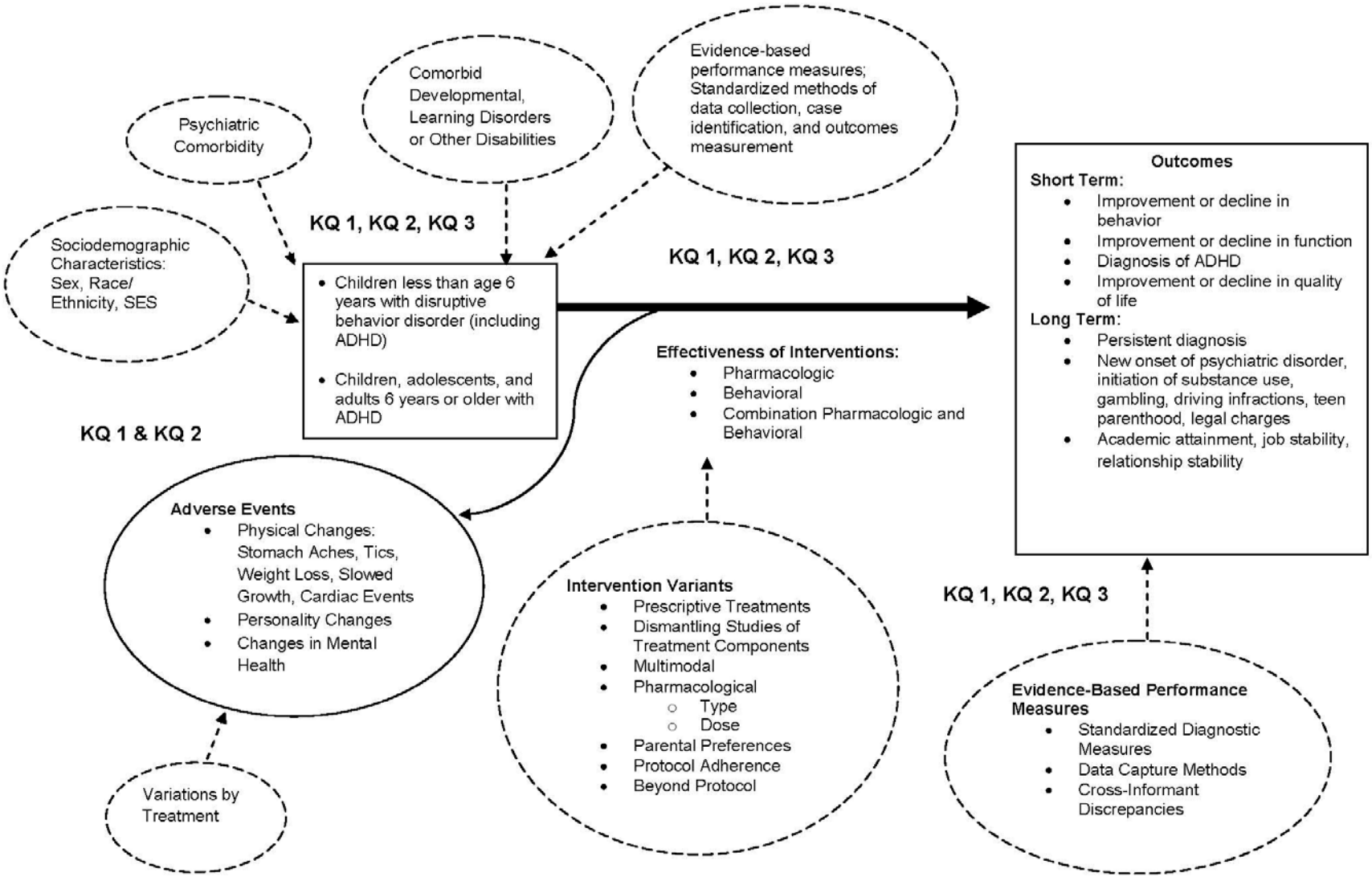
Evidence Gap	Relevant Key Question
Among children ages 6 years or older with ADHD, there is a paucity of research examining positive treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based intervention) alone or in combination with pharmacological interventions, and effects on specific subgroups.	KQ 2
For people ages 6 years or older with ADHD, few efficacy and effectiveness studies are available on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components based on the person's needs.	KQ 2
Among people ages 6 years or older with ADHD, there is a lack of high-quality studies on efficacy and effectiveness of biofeedback and working memory training.	KQ 2
Among individuals ages 6 years or older with ADHD, there is a paucity of studies documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions.	KQ 2
For people ages 6 years or older with ADHD, limited data are available examining longer term follow-up of psychosocial and pharmacological ADHD treatments with appropriate comparison groups for long-term outcomes including academic and educational outcomes.	KQ 2
Among people ages 6 years or older with ADHD, there is a paucity of prospective combination pharmacological studies (e.g., combination pharmacotherapy treatment) as well as studies that follow individuals no longer requiring medication.	KQ 2
For people ages 6 years or older, there is a lack of evidence to support standardized methods for improving adherence to ADHD medications.*	KQ 2
Among people ages 6 years or older with ADHD, there is a paucity of studies that examine mediators and moderators of positive treatment response. The extant literature provides limited information about variations in treatment response by specific sociodemographic characteristics (e.g., low socioeconomic status, gender, different racial or ethnic groups) and baseline clinical indices (e.g., comorbidity with other psychiatric disorders, ADHD subtypes, comorbid developmental disorders, comorbid learning disabilities, language impairments, reading or mathematics disorders).	KQ 2
For people ages 6 years and older with ADHD, standardized outcome measures such as global impairment scales, quality of life scales, and measures that capture school performance learning capacity, social and emotional functioning, social competence, and functional capacity are needed to compare study outcomes from different cohorts.	KQ 2
Research among people with ADHD ages 6 years and older that compares efficacy as measured by different data-capturing methods such as child self-rating scales, parent rating scales, and semistructured interviews is limited.	KQ 2
Research is limited on the direct and relative effects of discrepancies among multiple informants (e.g., parents, children, teachers, clinicians) on the diagnosis of ADHD and the effectiveness of treatments for people of all ages with ADHD.	KQ 2, 3
The extant literature lacks evidence-based measures for assessing prevalence and treatment outcomes for people of all ages with ADHD on a comparable metric. Standardized methods of data collection, case identification, and outcomes measurement in epidemiologic surveys and administrative databases are lacking, particularly for adolescents and adults.	KQ 3
There is a paucity of evidence examining the amount of variation in case identification and prevalence across geographic areas, age groups, settings, and cultures, as well as a lack of research examining the causes and consequences of such variation in children's access to treatment and outcomes.	KQ 3

Table A. Preliminary evidence gaps by Key Question (continued)

Evidence Gap	Relevant Key Question
Diagnostic tools and measurements for outcomes beyond behaviors associated with ADHD (such as social functioning/interaction with peers) are not standardized. This gap includes a need for brief instruments that can be used in generalizable practice settings including epidemiologically valid long-term cohort studies and practice-based research networks (PBRNs).*	KQ 3
Little research is available that addresses the etiology and consequences of geographic variation in treatment patterns of ADHD in all age groups in terms of effect on outcomes. These factors might include cross-sector coordination of health services, family and child factors, provider factors, and availability and type of insurance.	KQ 3
For people of all ages with ADHD, there is a paucity of comparative evidence from practice-based research regarding access to and the use of generalists in combination with specialists compared with referral to specialists in generalizable practice.*	KQ 3

*Evidence gaps added by the stakeholders during and after the first conference call.

Figure A. Analytic framework depicting relationships between Key Questions, populations, interventions, outcomes, and components of evidence gaps



Methods

Identifying Evidence Gaps and Developing PICOTS

We identified the initial evidence gaps from sections throughout the draft review that described limitations preventing the authors from drawing conclusions about a research question. The project team then used information from the draft review regarding eligible populations, interventions, comparators, outcomes, timeframes, and settings (PICOTS) to develop a table showing the relevant PICOTS for each evidence gap.

We identified potential stakeholders representing a broad range of interests and expertise. We scheduled two rounds of conference calls using GoToMeeting® and two rounds of prioritization with the stakeholder group. Prioritization involved using an online prioritization tool we developed that allowed the stakeholders to assign a limited number of 'stars' to gaps they considered the highest priority.

A preliminary list of evidence gaps and an analytic framework showing the relationships between the Key Questions, PICOTS elements, and components of the evidence gaps were presented to the stakeholders as part of their orientation materials and discussed at the first stakeholder call. During the first call, we invited stakeholders to comment on and make contributions to the list of evidence gaps. We also reviewed an inventory of ongoing research studies, developed by the project team through searching online research registries, to help identify new data that might be pertinent to evidence gaps. After receiving stakeholder input, project investigators revised the list of evidence gaps, and applied the PICOTS elements to the new and revised gaps.

Criteria for Prioritizing Evidence Gaps

To complement the stakeholders' own perspectives during the prioritization process, we provided the stakeholders with a modified version of the Effective Health Care (EHC) Program Selection Criteria.

Engaging Stakeholders to Prioritize Evidence and Develop Research Needs

After the first call, we asked the stakeholders to assign a limited number of stars to the gaps they viewed as the highest priority. During the second call, we reviewed and discussed the results of the first prioritization exercise, finalized the upper tier of evidence gaps, asked stakeholders for feedback on the PICOTS, and invited thoughts on potential research designs for these upper tier gaps. Following this discussion, we applied the updated PICOTS framework to the upper tier evidence gaps and translated them in to research questions. We then invited the stakeholders to reprioritize only the upper tier of the evidence gaps using the online tool to create a final list of prioritized research needs.

Developing Research Questions and Determining Potential Research Designs

We applied research design considerations to the top-ranked research needs. We did not ask stakeholders to rank research designs or provide input to the proposed research designs. The final

list of prioritized research needs was not shared with the stakeholders until the public comment period of the draft report.

Results

Prioritized Future Research Needs and Justification for Urgency

From the 29 original evidence gaps, eight were deemed by the stakeholders as the highest-priority research needs, representing roughly the top quartile of the original list (Table B). In this executive summary, we present the research need, the associated PICOTS, and the research teams initial views of the potential study designs that could be used to address the priority research need. A discussion of the potential study design considerations, including issues of validity, resources required, ability to recruit subjects or obtain data, and potential ethical, legal, or social issues, may be found in the full future research needs report.

Table B. Eight highest-priority research needs

Research Need
For people of all ages diagnosed with ADHD, what are the most accurate, brief standardized tools for diagnosis and outcome measurement that can be administered in generalizable practice settings and used on a repeated basis, integrated into clinical care?
For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy, effectiveness, and harmfulness of the available pharmacological treatments, singularly or in combination with other pharmacologic interventions?
For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness for patient outcomes of differing combinations of psychosocial and pharmacological treatments for those who either are initiating treatment with psychosocial therapies or who have not improved on their current therapy? Are there discrete patient-level predictors that favor a particular treatment strategy?
For people of all ages diagnosed with ADHD (and especially adolescents and adults), what methods provide the most useful data collection, assessment of prevalence, case identification, and outcomes measurements for studies involving epidemiologic surveys and administrative databases?
For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness of specific psychosocial treatments alone compared with pharmacological treatments alone or in combination with psychosocial treatments for patient outcomes?
For people ages 6 years or older with ADHD, what are the comparative long-term outcomes for the available psychosocial and pharmacological treatments?
Among children less than 6 years of age with disruptive behavior disorder or ADHD, what is the relative/comparative efficacy of key components of psychosocial treatment programs? These might include the relative efficacy of specific parent training compared with treatment components targeting the child, or the efficacy of variants in psychosocial treatment service delivery that allow flexibility for parental preferences compared with those that do not.
For people ages 6 years or older with ADHD, which specific sociodemographic, baseline clinical characteristics, and neurobiological features predict a positive treatment response with respect to patient outcomes?

Details of Future Research Needs

Research Need

- **For people of all ages diagnosed with ADHD, what are the most accurate, brief standardized tools for diagnosis and outcome measurement that can be administered in generalizable practice settings and used on a repeated basis, integrated into clinical care?**

P	I	C	O	T	S
All ages Diagnosed with ADHD	N/A	Feasible tools would be compared with reference standards for diagnosis, outcomes	Validation of instrument compared with reference standard	N/A	a) Epidemiological and naturalistic research settings b) Clinical trials (efficacy) c) Practice-based research settings (effectiveness)

Considerations for Potential Research Designs

- Psychometric testing

Research Need

- **For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy, effectiveness, and harmfulness of the available pharmacological treatments, singularly or in combination with other pharmacologic interventions?**

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or disruptive behavior disorder	Pharmacological treatments, as single agent and/or medication combination	Other single or combined pharmacological treatments (e.g. stimulants vs. nonstimulants)	Outcomes for children and parents such as*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence, and harms, such as behavioral side effects, sleep difficulties, appetite/metabolic concerns, and cardiovascular changes.

Considerations for Potential Research Designs

- Randomized controlled trials (RCTs)
- Retrospective cohort studies
- Meta-analysis of individual participant data

Research Need

- **For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness for patient outcomes of differing combinations of psychosocial and pharmacological treatments for those who either are <u>initiating treatment</u> with psychosocial therapies *or* who have <u>not improved on their current therapy</u>? Are there discrete patient-level predictors that favor a particular treatment strategy?**

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including Oppositional defiant disorder (ODD) and Conduct disorder (CD)	Initial treatment with psychosocial and/or pharmacologic treatments or Addition of a psychosocial and/or pharmacological treatment to an existing treatment after treatment failure	Initial treatment with psychosocial and/or pharmacologic treatments or Continuation of existing treatment without addition of psychosocial and/or pharmacologic treatment or switch to different treatment	Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence, and harms, such as behavioral side effects, sleep difficulties, appetite/metabolic concerns, and cardiovascular changes.

Considerations for Potential Research Designs

- Randomized controlled trials

Research Need

- **For people of all ages diagnosed with ADHD (and especially adolescents and adults), what methods provide the most useful data collection, assessment of prevalence, case identification, and outcomes measurements for studies involving epidemiologic surveys and administrative databases?**

P	I	C	O	T	S
All ages Diagnosed with ADHD	N/A	a) Education system, b) Health insurance, c) Providers	Evidence-based performance measures (Methods)	N/A	Population-based surveys

Considerations for Potential Research Designs

- Expert panel
- Secondary data analyses of epidemiological and treatment studies

Research Need

- **For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness of specific psychosocial treatments alone compared with pharmacological treatments alone or in combination with psychosocial treatments for patient outcomes?**

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including ODD and CD by DSM)	Psychosocial interventions alone (including parent training and school-based interventions)	Pharmacological treatments, alone or in combination with psychosocial treatments	Outcomes for children and parents*	6 Months/1 Year	Private clinic, community clinic

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

- Randomized controlled trials

Research Need

- **For people ages 6 years or older with ADHD, what are the comparative long-term outcomes for the available psychosocial and pharmacological treatments?**

P	I	C	O	T	S
Age ≥ 6 years Diagnosed with ADHD	Psychosocial and pharmacological treatments		Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence, and adverse events/harms.

Considerations for Potential Research Designs

- Extensions of RCTs
- Retrospective cohort study

Research Need

- **Among children less than 6 years of age with disruptive behavior disorder or ADHD, what is the relative/comparative efficacy of key components of psychosocial treatment programs? These might include the relative efficacy of specific parent training compared with treatment components targeting the child, or the efficacy of variants in psychosocial treatment service delivery that allow flexibility for parental preferences compared with those that do not.**

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including ODD and CD by DSM)	Variety of components as a part of a psychosocial treatment program	A different collection of components of a psychosocial treatment program so as to allow isolation of the effect of specific components	Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

- Randomized controlled trials

Research Need

- **For people ages 6 years or older with ADHD, which specific sociodemographic, baseline clinical characteristics, and neurobiological features predict a positive treatment response with respect to patient outcomes?**

P	I	C	O	T	S
Age ≥ 6 years Diagnosed with ADHD	Any treatment for ADHD	a) Inter-subgroup comparisons (e.g., male versus female) b) Subgroup versus all ADHD subjects(e.g., comorbidity versus no comorbidity, inattentive subtype versus combined subtype); c) Correlation with quantitative traits (e.g., neuropsychological dysfunction)	Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

*Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

- Secondary analysis of existing cohort studies and randomized trials
- Consensus conference

Discussion

The final list of research needs incorporated a broad spectrum of issues. The needs ranged from epidemiological considerations to more clinically or treatment-oriented issues. The final list includes two epidemiological needs involving all ages, four clinically oriented needs for the those below 6 years, and two issues for those ages 6 years and older. For the younger group, the stakeholders prioritized research needs that would guide the selection of the most efficacious and effective medication and psychosocial interventions. For the older age group, stakeholders prioritized a need for studies to evaluate the relationship between patient-level characteristics and

treatment response (similar to a need in the younger group) and one for the comparative evaluation of long-term outcomes.

We proposed RCTs as the optimal study design for many questions. However, trials designed to compare components of different interventions or those designed to evaluate the role of patient-level predictors on treatment response would require very large sample sizes, on the order of 500 to 600 participants. For comparison, the major longitudinal study of ADHD to date, the MTA, had a sample size of 579. It is possible that some of these questions could be evaluated with complex secondary data analysis techniques.

Challenges presented by this process include scheduling conflicts, which led to incomplete participation from some members. Other key challenges involved the need to create a list of clear, concise gaps and the need to remain faithful to the language and intent of the findings of the original ADHD review. Further, identifying appropriate cut points for priority levels is an ongoing challenge. Finally, the stakeholder process is not intended to delineate a numeric rank order of research needs and the final results all should be seen as highest priority needs.

Conclusions

In this project, we worked with a group of stakeholders to refine 29 identified research gaps and transform them into eight highest-priority research needs in the field of ADHD. These highest-level needs included a broad range of issues cutting across age range (above and below 6 years of age), key clinical issues, and epidemiological and measurement concerns. Within this group of eight, clear themes emerged: the need for improved measurement tools, more generalizable study populations and settings, longer follow-up periods, more understanding of patient-level predictors of response, and more comparative evaluation of psychopharmacologic, psychosocial, and combination interventions across age ranges. PICOTS construction aided our consideration of study design issues and our sample power analyses demonstrated the clear pragmatic barriers that many of the potential designs will present. Advanced secondary data-analysis methods may allow some of these complex questions to be addressed in a more cost-effective manner but will not be able to fully replace the need for new large, long-term trials to evaluate these complex research needs in ADHD.

Background

Context

This Future Research Needs (FRN) report is based on a draft Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review titled, "Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment."[1] The purpose of the review was to synthesize recent research regarding treatment for preschoolers, long-term effectiveness, and variability in prevalence, diagnosis, and treatment for people of all ages. The aims of the review were to (1) critically examine the comparative long-term effectiveness and adverse events of interventions for Attention Deficit Hyperactivity Disorder (ADHD) (pharmacological, psychosocial, or behavioral and the combination of pharmacological and psychosocial or behavioral interventions); (2) critically examine the effectiveness and adverse events of interventions in preschool children with clinically significant disruptive behavior, who are, therefore, at high risk for ADHD; and (3) summarize what is known about patterns of identification and treatment for the condition. The draft review is based on literature searches that were conducted on December 1, 2009. The review was posted for public comment in October 2010. Publication of the final review is in progress, which will include an updated literature search.

The review examined factors such as geography, sociodemographics, temporal aspects, and provider type. The Key Questions (KQs) for the review were as follows:

KQ 1: Among children less than 6 years of age with Attention Deficit Hyperactivity Disorder or Disruptive Behavior Disorder, what are the effectiveness and adverse event outcomes following treatment?

KQ 2: Among people 6 years of age or older with Attention Deficit Hyperactivity Disorder, what are the effectiveness and adverse event outcomes following 12 months or more of any combination of follow-up or treatment, including, but not limited to, 12 months or more of continuous treatment?

KQ 3: How do (a) underlying prevalence of ADHD, and (b) rates of diagnosis (clinical identification) and treatment for ADHD vary by geography, time period, provider type, and sociodemographic characteristics?

Importance of Disease

As noted by the authors of the original Comparative Effectiveness Review (CER)[1], some evidence suggests that rates of identification and treatment for people with ADHD have increased in recent years;[2-4] however, prescription patterns and variations indicate that increases in identification may be linked with changes in practice rather than an increase in the underlying prevalence of the disorder.[5,6] In fact, the underlying prevalence of the disorder in children appears to have been relatively stable since the 1980s, to the extent that it has been measured using identical methods.[7] Increases in identification and treatment have occurred primarily among girls and older children consistent with changes in clinical guidelines.[3,8] Increases in off-label prescription of psychotropic medications for very young children have also been observed, presumably for preschoolers identified with ADHD or disruptive behavior.[9]

Clinically significant ADHD is often associated with concurrent oppositional and aggressive behaviors, anxiety, low self-esteem, and learning disabilities. Symptoms generally interfere with academic and behavior functioning at school and may also disrupt family and peer relationships. ADHD begins before children enter school, although it is most commonly identified and treated in primary school, ages 7 to 9 years.[10] In the preschool age group, ADHD is characterized not only by impairment in attention span, excessive impulsivity, and overactivity but is also frequently accompanied by additional disruptive behavior symptoms, including severe temper tantrums; demanding, uncooperative behavior; and aggressiveness.[11] Although levels of symptoms decrease with age, the majority of children with ADHD continue to show impairment relative to same-age peers throughout adolescence and into adulthood. Estimates of prevalence of ADHD among adults worldwide is 2.5 percent.[12]

Multiple short-term studies show that psychostimulant medications such as methylphenidate (MPH), dextroamphetamine (DEX), or mixed amphetamine salts (MAS) effectively decrease the core symptoms of ADHD and associated impairment, and that they are generally well tolerated but can be associated with common side effects.[13] These studies are generally performed in school-age children, and there is less evidence in preschoolers[14] and adults.[15,16] Several extended release (XR) preparations of psychostimulants developed in recent years are aimed at improved adherence and symptom control throughout the day as well as decreased abuse potential.[17] Nonstimulants (e.g., alpha-adrenergic agents and atomoxetine [ATX]) have also been developed and found to be helpful in controlling symptoms with few adverse events.[18] However, in general the benefits of medications wear off when they are discontinued.

Because ADHD is a chronic disorder, many children, teens, and adults may stay on medications for years at a time, but little information is available to patients and physicians regarding long-term effects or the natural history of the disorder as children mature into adulthood. The 2003 United States National Survey of Child Health (NSCH) estimated that 4.4 million children ages 4 to 17 years of age in the United States had a diagnosis of ADD or ADHD, of whom 56 percent were currently taking medication.[19] The psychostimulants used to treat older children and adults with ADHD are not approved for use in children less than 6 years of age; therefore, treatments for this population emphasize nonpharmaceutical interventions prior to medication. Recent reviews of treatments for preschoolers with ADHD emphasize use of parenting interventions prior to medication based on general clinical consensus. However, little information exists that documents the effectiveness of either medication or nonmedication interventions for ADHD in this age group. Off-label use of medications in the preschool population is, however, common.[20]

Findings of the Draft Comparative Effectiveness Review

The authors of the draft ADHD review found that the evidence for KQ 1 supported the use of parent behavior training interventions for preschoolers as an effective intervention both for oppositional behaviors and for ADHD symptoms where measured, with no adverse events reported. The largest barrier to successful completion of the intervention is parent attrition. Preliminary efforts to examine modes of service delivery to accommodate parent preferences suggest that such adjustments do not interfere with effectiveness as long as the program is delivered as designed. For preschoolers, psychostimulant medications are also generally safe and efficacious for improving behavior and can provide benefits in addition to parent training. However, adverse events, especially irritability and moodiness, can lead to discontinuation over extended periods of time, and use for several months to a year affects growth rate to a small

degree. The addition of school-based interventions to parent training appears to be more useful for disadvantaged populations, although benefits diminish following discontinuation of the intervention.[1]

For KQ 2, the authors found that the long-term effectiveness and safety of several psychostimulants, ATX, and guanfacine XR have been examined prospectively in children over the age of 6 years and adolescents. All of these agents are efficacious for control of inattention and overactivity for extended periods of time, and few serious adverse events are noted. Fewer individuals discontinue psychostimulants and ATX than guanfacine XR due to adverse events. Placebo-controlled discontinuation trials are few, one in children receiving amphetamines, and two others after 1 year and again after 2 years of use in children receiving ATX. These trials suggest that some individuals continue to benefit and others no longer benefit, following 12, 15, or 24 months of continuous treatment with medication.[1]

Evaluation of long-term outcomes following interventions for ADHD is complex due to multiple patterns of services used. The best data are available through multiple publications produced by the 8-year follow-up of the Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder (MTA) study.[21] By 3 years after initiation, no single intervention group showed superior benefit, which is likely due to individuals obtaining a complex range of interventions in the community. The majority of children who received an intervention maintained improvements in functioning, although they were not improved enough to match nonclinical comparison groups. A small proportion returned to previous levels of poor functioning over time. No clear relationship was identified between duration of medication use and outcomes. Other cohort studies suggest that long-term use of medication improves grade retention and academic achievement, and may lessen onset of substance use disorders as well as oppositional defiant, conduct, anxiety, and depressive disorders.[1]

The findings for KQ 3 included results from a systematic review and meta-regression that placed the worldwide pooled prevalence estimate of ADHD among those 18 years of age or younger at 5.29 percent (95% confidence interval [CI]: 5.01-5.56), with more boys than girls identified and the highest rates of disorder occurring in the 5- to 10-year-old age group. Primary sources of variability were identified as methodological rather than geographic, and included differences in requirements for impairment, diagnostic criteria, and source of information. Fewer studies are available that document prevalence in adult, adolescent, or preschool age groups, which likely reflects a lack of clarity regarding current diagnostic criteria in these groups. Information about clinical identification and treatment (available through administrative and prescription data and health surveys) documents that psychostimulant use for ADHD increased throughout the early to mid-1990s and slowed in the late 1990s and early 2000s in the United States. Disparities are noted, with more boys than girls treated and more Caucasians than Hispanics or African-Americans receiving medication treatment once diagnosed in the United States. Rates of identification and treatment also vary from state to state. Nonpharmacologic interventions are not documented.[1]

Objective

The purpose of this future research needs (FRN) project is to work with a diverse group of stakeholders to: (a) identify the persisting evidence gaps that impede decisionmaking for clinicians, researchers, policymakers, and consumers, and (b) prioritize the stakeholders' research needs related to the prevalence, diagnosis, and treatment of ADHD in children and adults.

Evidence Gaps

The draft review identified several topics for which authors found little or no evidence to draw conclusions. We developed the list of evidence gaps in Table 1 based on information gleaned from the draft review. We then applied the PICOTS from the CER inclusion/exclusion criteria and developed an analytic framework to show the relationships between the evidence gaps, PICOTS, and Key Questions (Figure 1). We modified the list of evidence gaps after stakeholder engagement. The specific gaps changed or added by the stakeholders during and after the first conference call are indicated with an asterisk. The original list of evidence gaps gleaned from the review and presented to the stakeholders during the first conference call is in Appendix A.

Table 1. Preliminary evidence gaps by Key Question

Evidence Gap	Relevant Key Question
For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions.	KQ 1
For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs alone compared with pharmacological treatments, alone or in combination with psychosocial treatments.	KQ 1
Among children less than 6 years of age with disruptive behavior disorder or ADHD, there is a paucity of research examining positive child treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based interventions, or other cross-sector evaluations), alone or in combination with pharmacological interventions, and effects on specific subgroups.	KQ 1
For preschoolers with disruptive behavior disorder or ADHD, there are few efficacy and effectiveness studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components based on the child's needs.	KQ 1
Among people less than 6 years of age with disruptive behavior disorder or ADHD, there is a lack of high-quality studies on efficacy and effectiveness of biofeedback and working memory training.	KQ 1
Among children ages less than 6 years with disruptive behavior disorder or ADHD, there is a paucity of studies documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions.	KQ 1
For children less than 6 years of age with ADHD, there are limited data on the influence of parental preferences regarding treatment approaches or modes of service delivery on short- and long-term outcomes.	KQ 1
Among children less than 6 years of age with disruptive behavior disorder or ADHD, there is a paucity of studies that disassemble the key components of available psychosocial treatment programs (e.g., specific parent training techniques compared to treatment components targeting the child and variants in service delivery to accommodate parental preferences).	KQ 1
Conflicting results from treatment studies of children less than 6 years of age with disruptive behavior disorder or ADHD show improvements in ADHD symptoms when the parent behavior training protocol is flexible and when the protocol is not flexible. Among children less than 6 years of age with disruptive behavior disorder or ADHD, studies comparing the relative efficacy of flexible versus nonflexible parent behavior training protocols are currently not available.	KQ 1
There are limited data available from studies with appropriate comparison groups about long-term outcomes for preschool interventions.	KQ 1
Among children less than 6 years of age with ADHD, there is a paucity of prospective studies that compare the efficacy, effectiveness, and harms of single and/or combination pharmacotherapies with other single or combined pharmacotherapies (e.g., stimulants vs. nonstimulants).*	KQ 1

Table 1. Preliminary evidence gaps by Key Question (continued)

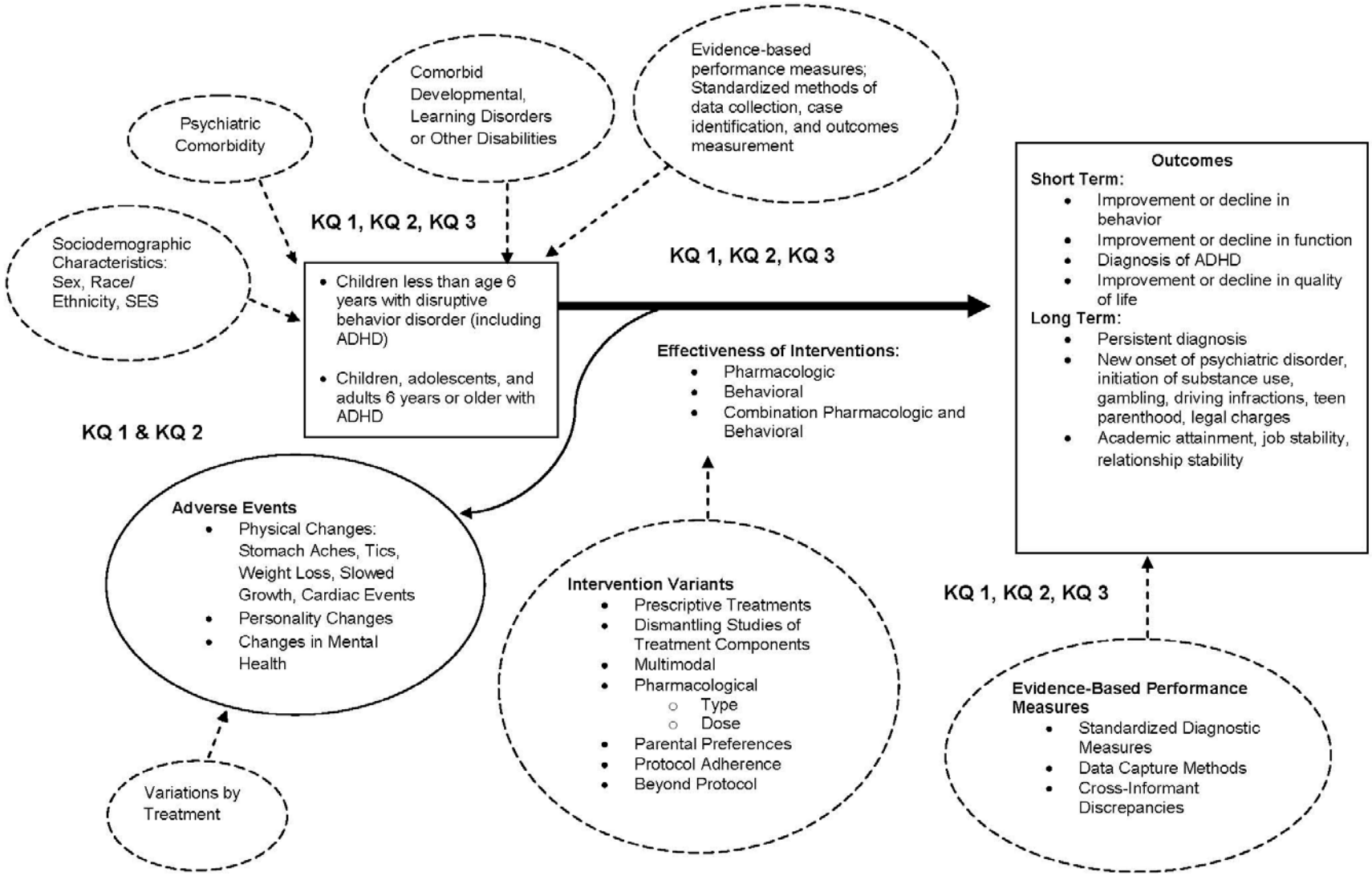
Evidence Gap	Relevant Key Question
For children ages 6 years or older with ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions.	KQ 2
For children ages 6 years or older with ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs alone compared with pharmacological treatments, alone or in combination with psychosocial treatments.	KQ 2
Among children ages 6 years or older with ADHD, there is a paucity of research examining positive treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based intervention) alone or in combination with pharmacological interventions, and effects on specific subgroups.	KQ 2
For people ages 6 years or older with ADHD, there are few efficacy and effectiveness studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components based on the person's needs.	KQ 2
Among people ages 6 years or older with ADHD, there is a lack of high-quality studies on efficacy and effectiveness of biofeedback and working memory training.	KQ 2
Among individuals ages 6 years or older with ADHD, there is a paucity of studies documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions.	KQ 2
For people ages 6 years or older with ADHD, there are limited data available examining longer term follow-up of psychosocial and pharmacological ADHD treatments with appropriate comparison groups for long-term outcomes including academic and educational outcomes.	KQ 2
Among people ages 6 years or older with ADHD, there is a paucity of prospective combination pharmacological studies (e.g., combination pharmacotherapy treatment) as well as studies that follow individuals no longer requiring medication.	KQ 2
For people ages 6 years or older, there is a lack of evidence to support standardized methods for improving adherence to ADHD medications.*	KQ 2
Among people ages 6 years or older with ADHD, there is a paucity of studies that examine mediators and moderators of positive treatment response. The extant literature provides limited information about variations in treatment response by specific sociodemographic characteristics (e.g., low socioeconomic status, gender, different racial or ethnic groups) and baseline clinical indices (e.g., comorbidity with other psychiatric disorders, ADHD subtypes, comorbid developmental disorders, comorbid learning disabilities, language impairments, reading or mathematics disorders).	KQ 2
For people ages 6 years and older with ADHD, standardized outcome measures such as global impairment scales, quality of life scales, and measures that capture school performance learning capacity, social and emotional functioning, social competence, and functional capacity are needed to compare study outcomes from different cohorts.	KQ 2
Research among people with ADHD ages 6 years and older that compares efficacy as measured by different data-capturing methods such as child self-rating scales, parent rating scales, and semistructured interviews is limited.	KQ 2
There is limited research on the direct and relative effects of discrepancies among multiple informants (e.g., parents, children, teachers, clinicians) on the diagnosis of ADHD and the effectiveness of treatments for people of all ages with ADHD.	KQ 2, 3
The extant literature lacks evidence-based measures for assessing prevalence and treatment outcomes for people of all ages with ADHD on a comparable metric. Standardized methods of data collection, case identification, and outcomes measurement in epidemiologic surveys and administrative databases are lacking, particularly for adolescents and adults.	KQ 3
There is a paucity of evidence examining the amount of variation in case identification and prevalence across geographic areas, age groups, settings, and cultures, as well as a lack of research examining the causes and consequences of such variation in children's access to treatment and outcomes.	KQ 3

Table 1. Preliminary evidence gaps by Key Question (continued)

Evidence Gap	Relevant Key Question
There is no standardization of diagnostic tools and measurements for outcomes beyond behaviors associated with ADHD (such as social functioning/interaction with peers). This includes a need for brief instruments that can be used in generalizable practice settings including epidemiologically valid long-term cohort studies and practice-based research networks (PBRNs).*	KQ 3
There is little research addressing the etiology and consequences of geographic variation in treatment patterns of ADHD in all age groups in terms of effect on outcomes. These factors might include cross-sector coordination of health services, family and child factors, provider factors, and availability and type of insurance.	KQ 3
For people of all ages with ADHD, there is a paucity of comparative evidence from practice-based research regarding access to and the use of generalists in combination with specialists compared with referral to specialists in generalizable practice.*	KQ 3

*Evidence gaps added by the stakeholders during and shortly after the first conference call.

Figure 1. Analytic framework depicting relationships between Key Questions, populations, interventions, outcomes, and components of evidence gaps



Methods

Identification of Evidence Gaps

We identified the initial evidence gaps from sections throughout the draft review that described limitations that prevented the authors from drawing conclusions about a research question.[1] The project team then used information from the draft review regarding eligible PICOTS to develop a table to show the relevant PICOTS for each evidence gap.

A preliminary list of evidence gaps (Appendix A) and an analytic framework (Figure 1) showing the relationships between the Key Questions, PICOTS elements, and components of the evidence gaps were presented to the stakeholders as part of their orientation materials and discussed at the first stakeholder call. During the first call, we invited stakeholders to comment on and make contributions to the list of evidence gaps. After receiving stakeholder input, project investigators revised the list of evidence gaps, and applied the PICOTS elements to the new and revised gaps to ensure that each gap addressed one or more populations, interventions, comparators, outcomes, timeframes, and settings within the scope of the review. The final list of evidence gaps and the analytic framework are presented above (Table 1 and Figure 1).

Criteria for Prioritization

After the stakeholders had an opportunity to revise the list of evidence gaps, the project team developed an online prioritization exercise (Appendix B) and invited the stakeholders to rank the evidence gaps in order of priority. We encouraged the stakeholders to consider their own perspectives and the interests of their constituents along with a modified version of the EHC Program Selection Criteria (Appendix C) and a list of ongoing studies relevant to the topics of the CER during the prioritization. The modified version of the EHC Program Selection Criteria emphasized the three elements that were most applicable to stakeholders considering future research needs on a topic already under review by the EHC. These elements were importance, desirability of new research/duplication, and potential impact. We did not ask the stakeholders to consider the other two elements of the EHC criteria, appropriateness and feasibility, at this juncture.

Before the prioritization exercise, the stakeholders also received a list of ongoing studies developed by the project team after reviewing titles and short descriptions of research studies obtained through searching online research registries. We searched clinicaltrials.gov, HSRProj, NIH RePORTER, and the International Clinical Trials Registry Project (ICTRP) to find relevant ongoing or recently completed research. Search strategies are shown in Appendix D. Two people from the research team independently reviewed each ongoing study title and abstract and applied the inclusion and exclusion criteria from the draft review to determine which studies might have met the inclusion criteria for the CER if they had been completed and published results before the CER cutoff date. During the first stakeholder call, the stakeholders reviewed the list of ongoing studies and provided feedback on its completeness and the relevance of the research studies to the existing evidence gaps. The purpose of this list was to help the stakeholders identify any potential evidence gaps that might be addressed by current research, and to use that information when considering how to prioritize the evidence gaps.

Engagement of Stakeholders, Researchers, and Funders

Because identifying and engaging a diverse stakeholder panel are critical components of the FRN process, we identified a broad range of interests and potential stakeholders as one of the first steps in this project. We identified potential stakeholders in consultation with our AHRQ Task Order Officer and during an internal planning meeting, to which we invited representatives from the EPC that produced the draft review. During the meeting, we discussed potential stakeholders known to the experts on our team; we also asked the review authors for names of stakeholders that they had used in generating their review. Each potential stakeholder completed a statement of disclosure, was screened for apparent conflicts of interest, and approved by AHRQ prior to the first stakeholder call.

We sought a variety of individuals who represented one or more perspectives on the issues of ADHD such as patient and family advocacy groups; health care providers, including diagnosticians and treatment experts; educators for preschool and school-age children; researchers, including those with experience in pharmacology, psychiatry, education, epidemiology, and screening tools; state policymakers and payers of services; professional provider and educator organizations; individuals with knowledge of health services delivery systems or disparities among patients with ADHD; and research funders. The purpose of seeking these different perspectives was to produce a group that represented varied points of view on issues related to treatment, diagnosis, adverse events, and prevalence with respect to ADHD.

After developing a list of potential stakeholders, we sent invitations to individuals and organizations to identify representatives. We provided potential stakeholders with a brief description of the project, including their role and the amount of time we expected them to contribute.

The stakeholders contributed to this FRN project via e-mail, conference calls, and Web-based prioritization activities. We planned two conference calls using GoToMeeting® and two rounds of a Web-based prioritization exercise with the stakeholder group. Prior to the first call, we sent orientation materials to the stakeholders. These materials included the executive summary of the draft review and a description of the FRN project and its goals. Stakeholders also received a meeting packet that included the preliminary list of evidence gaps, the modified EHC Program Selection Criteria, and a list of ongoing studies that were reviewed to determine if they meet the inclusion criteria for the review.

After the first and second conference calls, we accepted comments and edits via e-mail from the stakeholders on the list of evidence gaps and PICOTS documents that were discussed during the respective calls. These comments were reflected in changes to the pertinent documents and reflected in the meeting summaries.

Between the first and second calls, we asked the stakeholders to prioritize the revised list of evidence gaps. This exercise was the first round of prioritization, and it was based on the complete list of 29 evidence gaps. The second round of prioritization occurred after the second call, and consisted of only the top tier evidence gaps, or those that were ranked the highest in the first round (Appendix E). The Web-based prioritization exercises allowed each stakeholder to distribute a limited number of star-shaped indicators (referred to as stars in the remainder of this document) to those they viewed as the highest priority gaps. In the first round, we gave each stakeholder a total of 14 stars, which they could distribute among 29 gaps. No single gap could get more than four stars from a single person. In the second round, the stakeholders received nine stars to distribute among 16 evidence gaps, and no one gap could get more than three stars from a single person.

Prior to the second call, we sent the stakeholders the results of the first online prioritization exercise. For the upper tier, or highest-ranking, evidence gaps, we also shared the draft PICOTS. During the second call, we reviewed and discussed the results of the prioritization exercise and asked stakeholders for feedback on the PICOTS and for any thoughts on potential research designs for the upper tier evidence gaps. Following this discussion, we applied the updated PICOTS framework to the upper tier evidence gaps and translated them in to research questions. We then invited the stakeholders to reprioritize the upper tier of the evidence gaps using the same Web-based prioritization tool used in the first round. After the second round of prioritization, we identified the top-ranked research needs as determined by the stakeholders' prioritization. These are presented in this report as the prioritized future research needs for diagnosis, treatment, adverse events, and prevalence for ADHD.

Research Question Development and Research Design Considerations

After the second round of prioritization in which the stakeholders ranked the evidence gaps and identified the prioritized research needs, we applied study design considerations to the top-ranked research needs. In considering potential research designs, we concluded that for many research needs more than one research design can be applied. We considered the advantages and disadvantages of different factors for each potential research design over another. Such factors included advantages of the study design to produce a valid result; resource use, size, and duration; potential social, legal, and ethical issues; and availability of data or ability to recruit participants. We did not ask stakeholders to rank study designs or provide input to the proposed study designs, as such an exercise would add considerably to the length and complexity of the process, and some stakeholders might not have the technical expertise to engage in this process. The final list of prioritized research needs was not shared with the stakeholders until the public comment period of the draft report.

Results

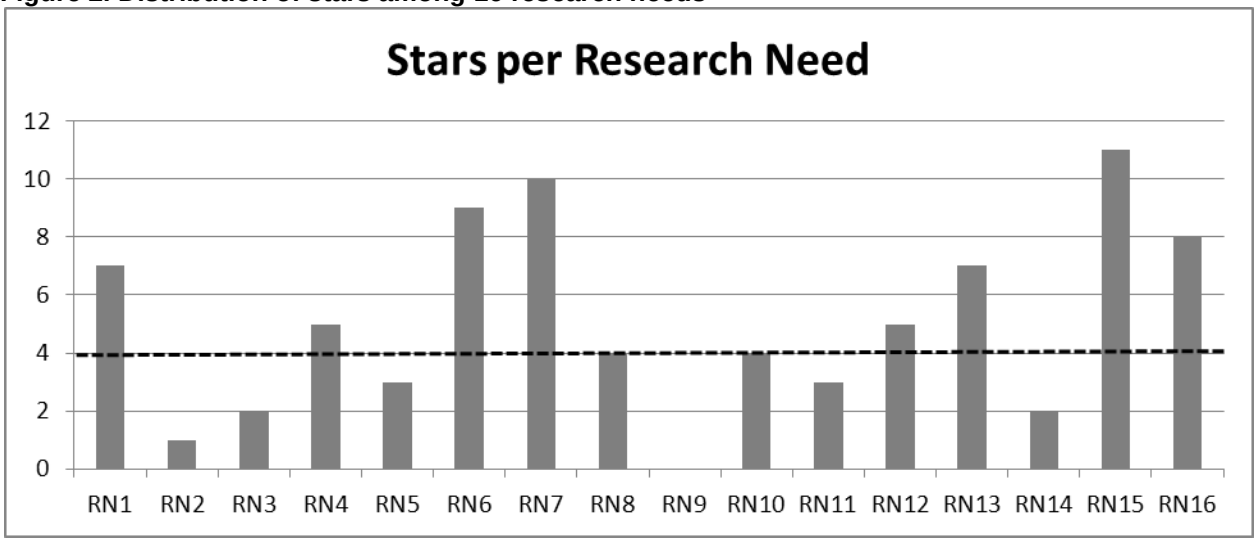
Research Needs

Prioritization Results

We conducted two rounds of prioritization to ultimately identify eight high-priority research needs. In the first round, the stakeholders determined that 16 of the 29 evidence gaps were of higher priority than the rest of the evidence gaps (Appendix E). Ten of the 12 stakeholders (83%) responded to the request to complete the first online prioritization exercise. The number of stars allocated to each evidence gap ranged from one to 10. Based on the distribution of the stars allotted to each gap, the upper-tier evidence gaps were the 15 gaps that received five or more stars. On reviewing the upper- and lower-tier gaps, the stakeholders requested that one of the lower-tier gaps be added to the upper tier and carried forward to the second round. This additional gap was one of two gaps that received four stars (Appendix E).

Between the first and second round of prioritization, the project team applied a PICOTS framework to the evidence gaps and transformed them into research needs presented in the form of questions. Appendix F shows the list of 16 research needs that the stakeholders prioritized in the second round. Results from the second round of prioritization (Figure 2) are based on responses from nine out of 12 stakeholders (75%). The number of stars allotted to each research need ranged from zero to 11. Out of 16 high-priority evidence gaps, eight were deemed by the stakeholders as the highest-priority research needs, representing essentially the top quartile of the original 29.

Figure 2. Distribution of stars among 16 research needs



The dashed line represents the cutoff point between the upper-tier and lower-tier research needs. All research needs with five or more stars represent the stakeholders' highest priorities.

Table 2 shows the eight highest-ranking research needs as determined by the second round of prioritization. Each of these received five or more stars. The number of stakeholders providing stars for each of the highest-ranking needs confirmed that these are of high priority for multiple stakeholders. For each of the eight highest-ranking needs, at least three stakeholders offered one

star and at least one of those gave the need two or more stars. In contrast, only one of the lower eight received more than one star from a single stakeholder, and that gap received only three stars in total from two stakeholders. Two of the highest-ranked research needs were focused on methods issues, and three on children younger than 6 years of age. These prioritized research needs span across all three Key Questions of the ADHD review.

Table 2. Eight highest-priority research needs

Research Need	# of Stars	# of Stakeholders Contributing at Least One Star
For people of all ages diagnosed with ADHD, what are the most accurate, brief standardized tools for diagnosis and outcome measurement that can be administered in generalizable practice settings and used on a repeated basis, integrated into clinical care?	11	6
For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy, effectiveness, and harmfulness of the available pharmacological treatments, singularly or in combination with other pharmacologic interventions?	10	7
For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness for patient outcomes of differing combinations of psychosocial and pharmacological treatments for those who either are initiating treatment with psychosocial therapies *or* who have not improved on their current therapy? Are there discrete patient-level predictors that favor a particular treatment strategy?	9	6
For people of all ages diagnosed with ADHD (and especially adolescents and adults), what methods provide the most useful data collection, assessment of prevalence, case identification, and outcomes measurements for studies involving epidemiologic surveys and administrative databases?	8	5
For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness of specific psychosocial treatments alone compared with pharmacological treatments alone or in combination with psychosocial treatments for patient outcomes?	7	5
For people ages 6 years or older with ADHD, what are the comparative long-term outcomes for the available psychosocial and pharmacological treatments?	7	4
Among children less than 6 years of age with disruptive behavior disorder or ADHD, what is the relative/comparative efficacy of key components of psychosocial treatment programs? These might include the relative efficacy of specific parent training compared with treatment components targeting the child, or the efficacy of variants in psychosocial treatment service delivery that allow flexibility for parental preferences compared with those that do not.	5	4
For people ages 6 years or older with ADHD, which specific sociodemographic, baseline clinical characteristics, and neurobiological features predict a positive treatment response with respect to patient outcomes?	5	3

Highest Priority Research Needs: PICOTS Information and Considerations of Potential Research Designs

For each of the highest priority research needs below, we have stated the need in the form of a research question, highlighted key points of the stated need, applied a PICOTS framework (indicating the population, intervention, comparator, outcome, time, and setting variables), and described considerations for potential research designs. Some needs address methodological rather than intervention issues and did not squarely fit into a PICOTS framework; in these instances, we have indicated that the column is not applicable (N/A). This top tier of research needs should be considered as a whole, without any particular ranking within this group implied.

When used in the following PICOTS frameworks to describe "setting", the term "clinic" indicates a private clinic (either pediatric or psychiatric), while the term "community" indicates a

community clinic (with uninsured or under-insured patients, again either pediatric or psychiatric). Stakeholders emphasized the need for the settings to be clinics similar to where most patients are seen, rather than academic health centers, laboratory classroom settings, or academic day care centers.

Research design considerations should be focused on feasibility and reducing bias as much as possible. We offer some considerations of potential research designs below each research need and PICOTS framework. For each potential research design we considered the following: advantages of study design for producing a valid result; resource use, size, and duration; availability of data and ability to recruit; ethical, legal, and social issues. These considerations are intended to raise issues for teams planning to address these research needs, and are not meant to be prescriptive.

Sample size is another important consideration in planning future research. Since sample size issues are common across many research needs, we have consolidated a discussion of sample size issues after the detailed descriptions of each research need. The sample size required for trials will depend on multiple factors, with 250 to over 1,000 subjects required to test many proposed research needs.

Research Need

- **For people of all ages diagnosed with ADHD, what are the most accurate, brief standardized tools for diagnosis and outcome measurement that can be administered in generalizable practice settings and used on a repeated basis, integrated into clinical care?**

Both the review and stakeholders emphasized the need for feasible and validated identification and management tools that are practical for use in the real-world clinic setting. One stakeholder emphasized the need for validated brief social functioning and peer interaction measures, specifically. A limitation is that a clear reference standard does not exist for social functioning measures.

P	I	C	O	T	S
All ages Diagnosed with ADHD	N/A	Feasible tools would be compared with reference standards for diagnosis, outcomes	Validation of instrument compared with reference standard	N/A	a) Epidemiological and naturalistic research settings b) Clinical trials (efficacy) c) Practice-based research settings (effectiveness)

Considerations for Potential Research Designs

Psychometric Testing

This type of rigorous evaluation would be an appropriate consideration for development of feasible and practical tools for use in diverse real-world clinical settings (clinical trials, practice-based research settings), particularly, for collecting adequate social functioning and peer interaction data. The preparation for such testing might require multiple steps, some qualitative and some quantitative, before some of the relevant tools are ready for validation in these settings.

- Advantages of study design for producing a valid result

    - These types of research designs can produce valid and reproducible results when conducted with appropriate measures to ensure an unbiased assessment of the tools being compared, such as randomization of order in which each tool is applied. Limitations include availability of feasible assessment tools and availability of a reference standard or validation.
- Ability to recruit/ availability of data
    - Given the varied settings in which ADHD is treated as well as the prevalence of this disorder, recruitment issues are minimal for most settings.
- Resource use, size, and duration
    - For primary data collection of this type, resource use and size are moderate and sample sizes needed depend on the number of items for the brief instruments. Brevity of measurement instruments will be key; use of computerized adaptive methods is a promising approach.
- Ethical, legal, and social considerations
    - Ethical, legal, and social considerations are minimal given there is not an intervention. Standard privacy and confidentiality issues and considerations are required.

Research Need

- **For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy, effectiveness, and harmfulness of the available pharmacological treatments, singularly or in combination with other pharmacologic interventions?**

This need focuses on pharmacologic interventions, either as a monotherapy or as a combination of pharmacologic agents, and broadly considers as key outcomes both the potential benefits and harms of interventions. We have identified key clinical and adverse events outcomes as reported in the draft review, which is limited by the variables reported in the published trials. ADHD, by nature, is represented by outcomes that are multifaceted. Stakeholders noted the need for greater information for each of these outcomes, and in particular noted a dearth of information regarding social functioning. Future studies might consider different or additional outcomes.

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or disruptive behavior disorder	Pharmacological treatments, as single agent and/or medication combination	Other single or combined pharmacological treatments (e.g., stimulants vs. nonstimulants)	Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence, and harms, such as behavioral side effects, sleep difficulties, appetite/metabolic concerns, and cardiovascular changes.

Considerations for Potential Research Designs

Randomized Controlled Trials

The strongest study design as regards validity is the randomized trial, to examine effectiveness of medication compared with placebo, in situations where current strength of evidence is low or insufficient, as well as comparative effectiveness of agents with each other.

- Advantages of study design for producing a valid result
  - RCTs will most completely control for selection bias and differential characteristics in treatment studies.
- Ability to recruit/ availability of data
  - Recruitment into RCTs can be challenging, but given the current use of these treatments in the younger population and the uncertainty regarding their effectiveness, multisite trials should be feasible.
- Resource use, size, and duration
  - Multisite, community-based trials will be optimal regarding assessment of treatment effectiveness, and therefore resource-intensive. See the following section regarding sample size estimates. Multisite studies will require careful training to assure consistency of intervention as well as analysis for site effect. Duration of the study would be several years at minimum.
- Ethical, legal, and social issues
  - Young children are a vulnerable population and careful informed consent will need to occur, but given the uncertainty regarding treatment choice in this population, high-quality trials are needed.

Retrospective Cohort Studies

Given the large sample size needed to detect relatively rare harms, prospective or retrospective cohort studies would be more feasible in assessing those outcomes.

- Advantages of study design for producing a valid result
  - Cohort studies may be larger, but are prone to selection bias since providers and families both choose and are aware of treatment. However, the ability to monitor generalizable populations allows sufficient power to detect uncommon harms. Propensity scoring or similar methods should be used for balancing on baseline characteristics.
- Ability to recruit/availability of data
  - Retrospective cohort studies of administrative or electronic health record data, which allows following large numbers of subjects over time. Such databases are becoming more commonly available and improving in quality. Such secondary data, however, may not be optimal for examination of drug benefits, which generally requires patient or patient derived information.
- Resource use, size, and duration
  - Resources required for secondary data analysis or meta-analysis at the individual level would be much less.
- Ethical, legal, and social issues
  - Data security and participant privacy/confidentiality issues require additional attention when obtaining data from other research groups. Pooling individual data

across trials may raise issues of intellectual property, but other fields have been able to accomplish such tasks.

Meta-Analysis of Individual Participant Data (MIPD)

If data were available and appropriate, meta-analysis of individual participant data might add to these analyses.

- Advantages of study design for producing a valid result
  - In an MIPD, individual data from existing studies are brought together using harmonized definitions, and re-analyzed, providing greater statistical power than the individual trials. Pooling data from multiple studies allow analysis of heterogeneous populations and increased power in analyses.
- Ability to recruit/availability of data
  - Eleven trials of pharmacologic interventions were reported in the meta-analysis, but there may be data availability issues regarding the ability to pool the information.
- Resource use, size, and duration
  - Resources required for secondary data analysis or meta-analysis at the individual level would be much less.
- Ethical, legal, and social issues
  - Data security and participant privacy/confidentiality issues require additional attention when obtaining data from other research groups. Pooling individual data across trials may raise issues of intellectual property, but other fields have been able to accomplish such tasks.

Research Need

- **For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness for patient outcomes of differing combinations of psychosocial and pharmacological treatments for those who either are <u>initiating treatment</u> with psychosocial therapies *or* who have <u>not improved on their current therapy</u>? Are there discrete patient-level predictors that favor a particular treatment strategy?**

This need addresses the question of the most effective combination of pharmacologic and psychosocial interventions, as either the *initial* line of treatment or as the option following failure of the current treatment. The assumption is that the standard of practice when initiating treatment for patients less than 6 years old with ADHD is to begin psychosocial treatment, but the question of interest for those beginning treatment is whether psychosocial treatment or pharmacologic treatment, singularly or in combination, is the optimal initial treatment. Initial combination treatments would be compared with initial treatments, and combinations after treatment failures would be compared with other combinations after treatment failures. This question is a complex one, involving a variety of potential combinations.

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including Oppositional defiant disorder (ODD) and Conduct disorder (CD) according to the Diagnostic and Statistical Manual (DSM))	Initial treatment with psychosocial and/or pharmacologic treatments or Addition of a psychosocial and/or pharmacological treatment to an existing treatment after treatment failure	Initial treatment with psychosocial and/or pharmacologic treatments or Continuation of existing treatment without addition of psychosocial and/or pharmacologic treatment or switch to different treatment	Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, behavior problems, social functioning, emotional regulation, executive functioning, treatment adherence, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

Randomized Controlled Trials

RCTs would provide information on comparative efficacy and effectiveness for patient outcomes of differing combinations of psychosocial and pharmacological treatments.

- Advantages of study design for producing a valid result
  - RCTs of variants of pharmacologic interventions are an ideal consideration because such designs can allow isolation of causal inferences related to pharmacological intervention being tested. Multiple-armed trials would allow testing of several hypotheses regarding relative efficacy of singular or combination treatment components.
  - RCTs provide ideal control for selection biases that can invalidate inferences made related to treatment. However, strong emphasis on controlling baseline covariates across treatment conditions and randomization can limit generalizability of results to other less controlled settings.
- Ability to recruit/Availability of data
  - Given the relatively high prevalence of ADHD for this age group, the availability of potential eligible patients is good. The specifics of selection criteria (e.g. prior treatment history, comorbid diagnoses, or concomitant medications) would affect the ease of recruitment.
- Resource use, size, and duration
  - Costs would be significant for such trials because they would be resource intensive and require both medication and psychosocial interventions, with a total sample size of N=840 with n = 210 per treatment arm) (Table 4). Also, trials to evaluate harms will require lengthy duration and large sample sizes.
- Ethical, legal, and social issues
  - Trials will require careful informed consent for this vulnerable population. Documentation of harm or adverse effects requires data and safety monitoring if evidence of significant benefit or harm is found.

Research Need

- **For people of all ages diagnosed with ADHD (and especially adolescents and adults), what methods provide the most useful data collection, assessment of prevalence, case identification, and outcomes measurements for studies involving epidemiologic surveys and administrative databases?**

This question is primarily one of research methods and highlights the need for tools to facilitate the efficient study of large-scale datasets, as well as conduct of primary data collection through surveys. Intervention and Treatment considerations are not a direct focus of this research need; rather, they are key in how to apply the findings that might result from acquiring these tools. The Setting consideration should maximize generalizability and reflect the population of children and young adults. Although a variety of tools are available, stakeholders indicated a concern that the datasets available may not contain the necessary data to capture the relevant information (e.g., diagnosis or clinical status). This need highlights the absence of validated, feasible tools for use in epidemiologic surveys and for secondary analyses of administrative or clinical datasets.

P	I	C	O	T	S
All ages Diagnosed with ADHD	N/A	a) Education system, b) Health insurance, c) Providers	Evidence-based performance measures (Methods)	N/A	Population-based surveys

Considerations for Potential Research Designs

One potential approach for this research need is not a research design, but rather a consideration for forming an expert panel to examine data sources such as third-party payer (e.g., private health insurance and state Medicaid) databases, electronic medical records, school records, and large epidemiological studies of children's health. The panel could bring together experts with knowledge of diagnostic codes, variables in databases, and access issues for school and medical records; epidemiologists and other researchers with knowledge of how to standardize data and use multiple data sources; and diagnosticians who specialize in screening and diagnosing ADHD in people of all ages. Consultation with privacy and information technology experts will also be helpful.

Expert Panel

- Advantages of study design for producing a valid result
  - A precondition for addressing this future research need would be collaborative relationships between researchers and entities that manage databases that could capture and contain the necessary information for assessing prevalence of ADHD, identifying undiagnosed cases, and determining appropriate outcome measures for people receiving treatment. Issues of data availability and data linkage will be as important as diagnostic criteria. The outcome would be consensus regarding data to be collected to address these prevalence and outcome research needs.
- Ability to recruit /availability of data
  - Recruiting experts for participation should be a relatively easy pursuit. Scheduling and managing deliverables for a large group could present challenges.
- Resource use, size, and duration

- Funding would need to be provided to an entity to provide staff and logistic support to the panel and it could involve travel costs for in-person meetings. Significant effort would be required to present information to this diverse group efficiently, as well as group process management to achieve consensus. A potential disadvantage is that an expert panel often takes a considerable amount of time to reach consensus and produce viable recommendations that can be put in to practice.

- Ethical, legal, and social issues
  - The panel could consider the ethical, legal, and social issues of secondary data analysis of large datasets with potentially identifying information and access to school and medical records. Panel members should include ethics and legal experts.

Secondary Data Analyses of Epidemiological and Treatment Studies

- Advantages of study design for producing a valid result
  - Consensus regarding methods for establishing diagnosis is a precondition for a major effort to conduct these secondary analyses. The use of diagnostic codes alone from administrative databases has, at best, unclear specificity in ADHD. For example, is a single diagnostic code sufficient to accurately identify ADHD, or should diagnosis on at least two occasions be required? A potentially sensitive and specific set of criteria could be developed through consensus development as described above. Another approach would be to link primary data collected from a registry as a reference standard to administrative data to examine the diagnostic characteristics of information from such administrative or other secondary data. Pooling data from observational studies allows for increased sample size and analysis of heterogeneous presentations of ADHD seen in various settings. Another advantage of secondary analytic studies that pool data from epidemiological and treatment samples is that sensitivity analyses could be conducted to determine which are the best capture methods and which are the most sensitive to picking up change due to an intervention. Subset analyses to examine the sensitivity of prevalence methods across demographic subpopulations will be important.
- Ability to recruit/availability of data
  - Success depends on the availability of large, comparable datasets. Many datasets exist, but the stakeholders raised concerns about the utility of the existing datasets to identify cases and assess prevalence. The consensus discussion noted above might clarify how useful the available data are.
- Resource use, size, and duration
  - Resources needed for such studies would be moderate, but the benefits would assist many future treatment efforts. A key goal will be to identify efficient methods of data collection and analysis for the future.
- Ethical, legal, and social issues
  - While secondary data analyses generally do not incur major ethical or legal issues, examination of the various components of ADHD may involve linking of administrative health data with, for example, school data. This procedure may require extensive consideration regarding need for parental consent in some settings and/or data use agreements prior to beginning data analysis.

Research Need

- **For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness of specific psychosocial treatments alone compared with pharmacological treatments alone or in combination with psychosocial treatments for patient outcomes?**

Either individual treatment or a combination of the two are relatively common interventions. While significant literature exists on the efficacy of psychosocial treatments, we currently know little regarding the comparative benefit of such behavioral and educational interventions compared to either medication treatment alone or to a combination of the two treatment type.

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including ODD and CD by DSM)	Psychosocial interventions alone (including parent training and school-based interventions)	Pharmacological treatments, alone or in combination with psychosocial treatments	Outcomes for children and parents*	6 Months/1 Year	Private clinic, community clinic

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

Randomized controlled trials

For this research need, randomized trials could be designed to test various components in a 2x2 matrix of psychosocial treatment variants (parent training, school-based intervention, combination, or pharmacological).

- Advantages of study design for producing a valid result
  - Randomized trials of variants of pharmacologic interventions are an ideal consideration as such designs can allow isolation of causal inferences related to the intervention being tested. Multiple-armed trials would allow testing of several hypotheses regarding relative efficacy of singular or combination treatment components. Similarly, such study designs can address any additive benefits or harms associated with addition of medication to a psychosocial intervention, compared with a psychosocial intervention alone. RCTs provide ideal control for selection bias. Community- based study settings and broad eligibility criteria will be critical to assure generalizability to the population of young children with the condition.
- Ability to recruit/availability of data
  - ADHD is a common condition in this age group with uncertainty regarding treatment choice; the study designs here are CERs in which all arms receive some treatment. This will aid recruitment.
- Resource use, size, and duration
  - This design approach would be resource intensive, as differences among the groups may be difficult to detect without a sufficiently large sample size (N =840; n = 210

per treatment arm) (Table 3). However, ADHD is common and currently incurs large health care and social costs, justifying an adequately powered trial. Multisite trials will be needed, increasing management complexity of the studies. Assessment of outcomes such as school achievement will require follow-up of several years.

- Ethical, legal, and social issues
  - Young children are a vulnerable population and careful informed consent will need to occur, but given the uncertainty regarding treatment choice in this population, high-quality trials are needed.

Research Need

- **For people ages 6 years or older with ADHD, what are the comparative long-term outcomes for the available psychosocial and pharmacological treatments?**

This need highlights the import noted by both the review and the stakeholders on the need for longer-term outcome data to guide decisionmaking. Outcomes of interests would involve both benefits, including educational measures that encompass academic outcomes, and harms. The definition of "long term" is not clear, but would likely be multiple years.

P	I	C	O	T	S
Age ≥ 6 years Diagnosed with ADHD	Psychosocial and pharmacological treatments		Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence., and adverse events/harms.

Considerations for Potential Research Designs

Extensions of RCTs

This research design could be applied to current or future RCTs by adding extension phases in which treatments are continued for some or all of the trial participants beyond the original timeline of the trial.

- Advantages of study design for producing a valid result
  - This research design is likely to yield long-term data on health outcomes and harms for various treatments. Significant crossover may occur over time, reducing the statistical power of the result. At some point, the original trial becomes similar to an observational cohort.
- Ability to recruit/ availability of data
  - Recruitment might depend on the overall attrition in the original RCT and retention over time is an issue in an extension period. Data could be biased toward those who experience benefits from treatments and in some cases, an appropriate comparison group may be lacking.
- Resource use, size, and duration
  - Extension studies could be expensive and resource intensive depending on the intervention and data collection methods. The optimal duration for observing long-term outcomes is not known, but generally 3 to 5 years is considered the minimum.
- Ethical, legal, and social considerations

- These studies would be most likely to compare active controls or to observe a group of people who are all receiving the same treatment because there are ethical concerns about withholding potentially beneficial treatment from a control group.

Retrospective Cohort Study

- Advantages of study design for producing a valid result
  - This research design has the potential to yield information about associations between treatments and outcomes or adverse events. Information may be available from more generalizable populations.
  - However, conclusions about causation must be made with caution. Because treatments are not randomized in this study design, a risk of bias exists that would need to be addressed in any analysis of the data. Many patients and providers are likely to switch treatments if patients experience harmful side effects early in treatment, making it difficult to assess long-term outcomes. Potential confounders (e.g., co-interventions, parental preferences) might not have been measured.
- Ability to recruit/ availability of data
  - Providers who treat people with ADHD could readily identify their patients with a diagnosis of ADHD and match them with appropriate controls and conduct retrospective records reviews.
  - However, as noted by the stakeholders, databases and medical records may lack the necessary data to sufficiently identify people with ADHD solely by reviewing records or mining databases. In situations where cases are known, the medical records may lack information about outcomes or adverse events. Access to adequate educational/academic outcome data could be difficult in a retrospective study.
- Resource use, size, and duration
  - Relative to an RCT, this study design would require fewer resources and take less time.
  - However, the sample size would have to be large to detect an association between specific treatments and outcomes, which would include measures of clinical benefits or harms.
- Ethical, legal, and social considerations
  - Issues of informed consent or waiver of consent would need to be negotiated. Linking of data across clinical and school records would require data use agreements.

Research Need

- **Among children less than 6 years of age with disruptive behavior disorder or ADHD, what is the relative/comparative efficacy of key components of psychosocial treatment programs? These might include the relative efficacy of specific parent training compared with treatment components targeting the child, or the efficacy of variants in psychosocial treatment service delivery that allow flexibility for parental preferences compared with those that do not.**

In this research need, stakeholders emphasized the importance of identifying what key parts of the psychosocial intervention were associated with improved outcomes, since these interventions currently contain a number of 'bundled' components. Specifically, they described dropout as a substantial concern and highlighted the need for a better understanding how

adherence relates to outcomes. In particular, they indicated that parental preference may be an influential factor. Given the complexity of the study design, we recommend a randomized trial design; other study types would have sufficient issues with selection bias and intervention description, making the ability to achieve a valid result problematic.

P	I	C	O	T	S
Age < 6 years Diagnosed with ADHD or at risk for ADHD or diagnosed with Disruptive Behavior Disorder (including ODD and CD by DSM)	Variety of components as a part of a psychosocial treatment program	A different collection of components of a psychosocial treatment program so as to allow isolation of the effect of specific components	Outcomes for children and parents*	Months /Years	Private clinic, community clinic, school, home

*Outcomes for children and parents include change in ADHD symptoms, social functioning, emotional regulation, executive functioning, treatment adherence, behavior problems, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

Randomized Controlled Trials

- Advantages of study design for producing a valid result
  - An RCT designed to test various components of a 2x2 matrix of psychosocial treatment variants, such as parent training, school-based intervention, or a combination of psychosocial treatments, while the comparison condition is centered on psychosocial treatment that includes flexibility with treatment manual to accommodate parental preferences would isolate treatment effects and the influence of parental preferences. See Table 3 in sample size section. Since all children would receive an active intervention, the effect of both interventions might be similar. An important consideration would be identification of an effect size between the groups that would be of clinical and policy significance prior to study initiation to reduce risk of type 2 error.
- Ability to recruit/ availability of data
  - ADHD is a common condition in this age group, and acceptability of educational and psychosocial interventions may be good. Fidelity of the intervention across sites and dropout will represent significant challenges to conduct of these trials. Multisite trials will be needed.
- Resource use, size, and duration
  - This design option would require a sample size of at least N=520 with about n=130 participants per intervention arm (Table 3), similar to the sample size used in the MTA study (579 children among 4 treatment groups).[22] Thus, given the number of participants and variety of treatment approaches (parent training, classroom, pharmacological, parental preference variant), this option would be expensive. ADHD is a common condition with significant treatment and social costs, justifying the need for such trials. Particularly attractive would be comparison of relatively simple, very standard interventions with interventions that are modified based on parental preference. The latter interventions are more complex and resource intensive to perform, making them important issues for evaluation.
- Ethical, legal, and social considerations

- Children would all receive treatment, reducing any ethical concerns regarding lack of equipoise.

Research Need

- **For people ages 6 years or older with ADHD, which specific socio-demographic, baseline clinical characteristics, and neurobiological features predict a positive treatment response with respect to patient outcomes?**

Note: Sociodemographic and baseline clinical characteristics include: gender, socioeconomic status, race, comorbidity with other psychiatric disorders, ADHD subtypes, comorbid developmental disorders, comorbid learning disabilities, language impairments, reading or mathematics disorders. The goal, in contrast to several other future research needs, is not to determine an overall effectiveness of treatment, but rather identify predictors of response to a treatment. Neurobiological features include: genetic variants and neuroimaging abnormalities. This need reflects stakeholders' interest in finding variables that might help tailor a recommendation of a particular treatment from which an individual would be more likely to receive benefit. Analyses would involve consideration of moderators and mediators.

P	I	C	O	T	S
Age ≥ 6 years Diagnosed with ADHD	Any treatment for ADHD	a) Inter-subgroup comparisons (e.g., male versus female) b) Subgroup versus all ADHD subjects(e.g., comorbidity versus no comorbidity, inattentive subtype versus combined subtype); c) Correlation with quantitative traits (e.g., neuropsychological dysfunction)	Outcomes for children and parents*	Months/ Years	Private clinic, community clinic, school, home

* Outcomes for children and parents include change in ADHD symptoms, behavior problems, social functioning, emotional regulation, executive functioning, treatment adherence, global functioning, academics, and parent competence.

Considerations for Potential Research Designs

Secondary Analysis of Existing Cohort Studies and Randomized Trials

- Advantages of study design for producing a valid result
  - Current published trials have had limited generalizable information regarding predictors of treatment response. Requests to investigators regarding additional information could be investigated. Secondary analyses of trials, which generally have higher quality and more standard data collection, would yield more valid results. Secondary analyses of existing cohort studies, in which patient characteristics are more reflective of the population affected by ADHD, will be more generalizable but likely have more incomplete data and potential selection bias.
- Ability to recruit/ availability of data
  - Completeness of data across different trials may be a challenge, and the willingness of researchers to share data can be an issue vis-à-vis control and intellectual property. Support of funders and professional societies can be valuable in accomplishing these

tasks. The ability to combine data across databases will depend on how much missing data are present, and whether the manner of data collection is heterogeneous.

- Resource use, size, and duration
  - These analyses are much less resource intensive than new, prospective data collection. Significant effort, however, must take place early on in the process to determine the feasibility of drawing inferences from data collected by different investigators from somewhat different populations. Duration of the study is modest, but experience has demonstrated that often at least a year is needed to assemble these secondary data from multiple sources.
- Ethical, legal, and social considerations
  - Since new data are not collected, only modest ethical issues are present. However, data control and intellectual property issues often require negotiation. Linkage of databases, especially those that contain genetic information, requires significant human subjects and data use agreement discussion.

Consensus Conference

A recommendation, not tied to a specific study design, would be researchers' consensus regarding routine collection of patient baseline clinical characteristics for future studies, which would greatly facilitate progression toward more patient-centered and personalized care for ADHD. This discussion would involve not just the types of variables collected, but also the specific categories and measures. Consensus across research organization and recommendations by funders would be helpful in advancing this research need. A consensus conference would be useful to accomplish this aim, since many of the problems enumerated above are due to the lack of standard data collection across studies. All such consensus efforts trade off complete data availability with cost of additional data collection. Brief, but consistent data collection regarding these issues across trials would greatly aid addressing this research need.

Sample Size Calculations

Power analyses were conducted based on a few hypothetical designs for randomized trials that would fit one or more of the research needs outlined in this report. Some of the high-priority research needs involve tests of larger effects (e.g., treatment main effects, comparisons to usual care), whereas others involve comparisons of smaller effects (e.g., treatment interactions, comparisons between treatments). Also, the earlier comparative effectiveness review found a wide range of effect sizes for medications and psychosocial interventions compared with no treatment, to treatment as usual, or to each other. Therefore, rather than make strict assumptions about the treatments being tested, we estimated the sample size required for testing both main effects and interaction effects, and we allowed for a range of effect sizes (.2, .35, .5, .8). We focus on the 2x2 factorial design since it was a component of several high-priority research needs.

These power analyses were conducted using simulations.[23] Table 3 shows the sample size required to detect treatment main effects and interaction effects on a normally distributed continuous outcome (e.g., pretest to posttest change) with a 2x2 factorial design in which individuals are randomly assigned to treatment. Each sample size was determined by generating 2,000 simulated datasets and identifying the minimum sample size required to detect the given effect with 80% power, 5% Type I error, and a 2-tailed test. The data generation model assumed equal effect sizes for the two treatments and their interaction:

$$Y_i = \mu + d*Z1_i + d*Z2_i + d*Z1_i*Z2_i + e_i$$

where Y_i is the outcome for person i, μ is the pre-treatment mean, d is the size of the two treatment main effects and their interaction effect (relative to the control group standard deviation on the change score), $Z1_i$=1 if person i received treatment 1 and $Z1_i$=0 otherwise, $Z2_i$=1 if person i received treatment 1 and $Z2_i$=0 otherwise, and e_i is the residual for person i.

Table 3. Sample size required to detect treatment effects in a 2x2 factorial design

Effect	Effect size	Approximate n per treatment arm	N
Treatment main effect	0.20	395	1580
Treatment main effect	0.35	130	520
Treatment main effect	0.50	70	280
Treatment main effect	0.80	30	120
Interaction	0.20	800	3200
Interaction	0.35	260	1040
Interaction	0.50	130	520
Interaction	0.80	50	200

To detect treatment main effects, a 2x2 factorial design requires the same sample size per treatment arm as a two-group study. (The factorial design simply has four treatment arms in order to detect two different treatment main effects.) To detect an interaction between two treatments (or between a treatment and an effect modifier), the required sample is about twice as large as the sample required to detect a treatment main effect of the same size (Table 3). Of course, detecting a smaller treatment effect requires a larger sample.

Table 4 shows that taking more than two measurements of the outcome variable during the intervention period reduces the required sample size. These results are based on simulations similar to those described above. We assumed a constant effect size of .35 (from the first measurement occasion to the last) for the treatment main effects and their interaction.

Table 4. Sample size required to detect treatment effects in a 2x2 factorial design with repeated measures

% variation between individuals	Effect	# repeated measures	Approx. n per treatment arm	N
20	Treatment main effect	2	215	860
20	Treatment main effect	3	210	840
20	Treatment main effect	5	170	680
20	Treatment main effect	7	135	540
20	Treatment main effect	9	115	460
20	Interaction	2	400	1,600
20	Interaction	3	420	1,680
20	Interaction	5	340	1,360
20	Interaction	7	260	1,040
20	Interaction	9	220	880
50	Treatment main effect	2	140	560
50	Treatment main effect	3	135	540
50	Treatment main effect	5	110	440
50	Treatment main effect	7	90	360
50	Treatment main effect	9	70	280
50	Interaction	2	260	1,040
50	Interaction	3	250	1,000
50	Interaction	5	210	840
50	Interaction	7	170	680
50	Interaction	9	140	560

Table 4. Sample size required to detect treatment effects in a 2x2 factorial design with repeated measures (continued)

% variation between individuals	Effect	# repeated measures	Approx. n per treatment arm	N
80	Treatment main effect	2	60	240
80	Treatment main effect	3	60	240
80	Treatment main effect	5	45	180
80	Treatment main effect	7	40	160
80	Treatment main effect	9	30	120
80	Interaction	2	110	440
80	Interaction	3	110	440
80	Interaction	5	80	320
80	Interaction	7	70	280
80	Interaction	9	60	240

In a trial with repeated measures, the amount of between-subject (versus within-subject) variation in the outcome variable affects projections of the required sample size. Having a larger proportion of variation between subjects corresponds to less residual error and easier detection of treatment effects. The proportion of variation that is between subjects depends on the outcome being studied, the reliability of the outcome measures, and the amount of time between measurements. We used a range of values (.2, .5, .8).

The data generation model for repeated measures designs included a random intercept to account for the dependence among multiple observations per person. The model assumed that there was no main effect of time on the outcome:

$$Y_{it} = \mu + (d/(T-1))*Z1_i*time_{it} + (d/(T-1))*Z2_i*time_{it} + (d/(T-1))*Z1_i*Z2_i*time_{it} + u_{0i} + e_{it}$$

where Y_{it} is the outcome for person i at time t, μ is the pretreatment mean, d is the size of the two treatment main effects and their interaction effect (relative to the control group standard deviation on the dependent variable), T is the number of measurement occasions, $Z1_i$=1 if person i received treatment 1 and $Z1_i$=0 otherwise, $Z2_i$=1 if person i received treatment 1 and $Z2_i$=0 otherwise, $time_{it}$={1,…T} is time since the beginning of the study, u_{0i} is a person-level random intercept, and e_{it} is the residual for person i at time t.

As shown in Table 4, increasing the number of measurement occasions reduces the sample size required to detect a treatment effect of a given size. In deciding on the number of measurement occasions in a study, one must weigh the cost of adding participants against the cost of additional data collection. (Because the two data generation models are based on different assumptions and have different denominators for the effect size, the sample size requirements for a design with d=.35 and two repeated measures are different in Table 4 than in Table 3).

Discussion

The purpose of this project was to utilize a structured approach to further refine and prioritize specific areas of future research in the area of ADHD that were necessary to sufficiently address Key Questions in the review, "Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment."[1] This project worked to clearly identify evidence gaps described in the report, work with stakeholders to prioritize this list of gaps and transform them into research needs, further prioritize these needs, and consider PICOTs and potential future study designs for the highest prioritized needs.

In regards to our structured stakeholder engagement process, we were grateful to the diverse and enthusiastic team of individuals who provided the needed depth of knowledge in the broad and complex field of ADHD. The stakeholder group included clinicians, advocates, researchers, education specialists, and funders. Our conference calls before and after the first round of prioritization revealed several key themes that helped inform our development of the gap list. These themes included a desire for improved generalizability of study populations and settings, emphasizing comorbidity over diagnostic purity and community-based settings over traditional academic or industry-based research clinics. They emphasized the importance of longer-term study periods (years versus months) and made special note of the desire for epidemiological long-term studies akin to The Framingham Study,[24] well known in the field of cardiovascular health. They also highlighted a concern about high dropout rates and indicated an interest in better understanding how adherence to interventions influences outcomes. A final theme that emerged was the desire for a better understanding of how patient-level predictors might influence treatment choice. This process of refinement helped create a list of 29 research gaps that were based on those derived from the initial ADHD evidence review but also reflected the perspectives of the stakeholders. Our initial prioritization exercise revealed 16 higher-priority gaps that were converted into 16 research needs.

The final list of eight highest-ranking research needs incorporated a broad spectrum of issues. The needs identified ranged from epidemiological considerations to more clinically or treatment-oriented research needs. Two epidemiological needs were identified. The first involved the need for identification of best *methods* for data collection, prevalence assessment, case identification, and outcomes measurement for studies involving epidemiologic surveys and administrative databases. The second epidemiological need centered on the desire for accurate and brief standardized case identification and outcome measurement tools designed for use in practice-based research settings and actual clinical practice.

The more clinically oriented needs included four issues from the younger age group (below 6 years) and 2 issues from older age group (6 years and older). For the younger group, the stakeholders prioritized the need for efficacy and effectiveness studies of medication, both alone and in combination. In conference call discussions, stakeholders had indicated concern that combination pharmacotherapy has not been evaluated in the younger age group, yet is known to occur frequently in practice. They also ranked highly the need for efficacy and effectiveness studies of medication and psychosocial interventions alone or in various combinations with one another. Also in conference calls, stakeholders discussed the desire for a large, long-term, multisite trial comparing medication to psychosocial intervention with combination treatment for the younger age group. The stakeholders also prioritized a need to develop studies that would evaluate what types of unidimensional (psychosocial intervention alone) or multidimensional (psychosocial with medication) treatment packages are optimal for *certain subgroups* of children

under the age of 6 years. For example, what types of interventions are best for treatment-naïve individuals and what might be best for treatment nonresponders? And, how do patient-level characteristics such as sex, socioeconomic status presence of comorbidities such as learning disorders or anxiety disorders affect the effectiveness and choice of treatment? Finally, for the younger group, the stakeholders emphasized with their ranking the need to disaggregate psychosocial treatment packages into their subparts (e.g., child-focused interventions, school-based behavioral intervention, parent training) and evaluate their relative efficacy.

For the older age group (6 years of age and older), one of the more clinically oriented research needs revealed a desire for studies that would evaluate the relationship between patient level characteristics and treatment response. Similar to the research need described above regarding optimal treatments for those less than 6 years of age, this need reflects an interest in identifying whether patient-level characteristics can inform selection of specific interventions. This area of needs perhaps points to a recognition that the complexity of the field and heterogeneity of those affected by ADHD may well demand a more personalized approach to intervention choice in the future. Finally, for the older age group, the stakeholders prioritized the need for studies that allow for the comparative evaluation of long-term outcomes such as educational/academic outcomes, social functioning, employment outcomes, and criminality.

In our consideration of potential study designs, we proposed RCTs as the optimal study design for many questions. Our consideration of relevant design characteristics and sample size was informative to illustrate the wide range of complexity and resources that would be required to undertake some of the potential trial designs. For example, single and combination pharmacotherapy efficacy trials for children less than 6 years of age are likely challenged by the demands of long-term follow-up more so than design complexity and sample size demands. However, trials designed to compare types of interventions (*for example, comparing subcomponents of psychosocial intervention packages*) or those designed to evaluate the role of patient-level predictors on treatment response would require very large sample sizes. This holds true even when considering theoretical high levels of repetition of measures during the study period. Even when the known effect sizes of the compared interventions is large, the sample size requirements may prove prohibitive. In such cases, sample size and cost will need to be weighed carefully against the importance of the research question. Any part of this consideration would also need to address bioethical concerns of trials involving those less than 6 years of age.

It is possible that some of these questions could be evaluated with complex secondary data analysis techniques. Meta-analysis is a commonly employed tool in comparative effectiveness research but may not be a feasible tool in all situations because of a lack of studies in an area or because of the heterogeneity of populations and measurement tools across existing studies. However, in some situations where original raw data from previously completed studies could be shared between investigators, advanced techniques of data pooling could potentially be utilized to deal with the heterogeneity problem. This pooling may allow researchers to ask comparative effectiveness questions and perform subgroup analyses without conducting new large trials in some situations. This set of data pooling techniques when employed in the psychological sciences is sometimes termed Integrative Data Analysis.[25]

The nature of the stakeholder process is associated with certain limitations. While stakeholder input was valuable, scheduling challenges led to incomplete participation from some members. To accommodate stakeholder schedules, we provided multiple time slots for the calls, meaning that the stakeholder group was not identical on each call. Despite the group's clear general collegiality, some calls were dominated by stakeholders who were more naturally

inclined to present their opinions, which may have led to the crowding out of the opinions of others. Because of this common characteristic of such group processes, we encouraged stakeholders to e-mail thoughts to the study team, and we received multiple communications. Other key challenges related to gap development and presentation. The process created a challenging tension between the need to create a list of clear, concise gaps and the need to remain faithful to the language and intent of the findings of the original ADHD evidence review. Although this balance was difficult to strike, it may represent a strength of the process in that neither the findings of the systematic review nor the views of the stakeholder panel fully dominate the final product. Finally, our report was based on a draft of the final ADHD CER, so specifics of the final report may slightly differ from what we report here.

We organized the gaps by Key Questions from the original ADHD review. Thus, some gaps may have appeared quite similar with differences only in the age range of the target study population, for example. This required that stakeholders take careful note of the subtleties between some gaps and needs when going through the ranking exercises. Some stakeholders may have been more accustomed to considering research gaps and needs from their particular field of work and might have found it difficult to interpret and prioritize research questions developed and organized by other authors. Our research team and the stakeholders raised the question of whether gaps might be made more digestible if organized by theme or domain (for example, one proposed schema broke the gaps into methodologic, treatment intervention oriented, and outcome oriented). How to best organize a list of gaps for presentation to a group of stakeholders for their consideration remained a question for the team at project completion and will be an important ongoing issue for future FRN projects. We chose not to stratify the needs by area, since the stakeholders might view some content areas as more important than others. In relation to prioritization exercises and interpretation of voting results, the dominant challenge was in identifying appropriate cut points for priority levels. We worked to minimize the risk of deprioritizing gaps or needs arbitrarily by erring on the side of inclusion when cut points were not clear. The stakeholder process is not intended to delineate a clear rank order of research needs. However, the structured process used in this project may prove to be a viable way of reaching relative consensus on research priorities in this broad and complex topic area.

Conclusions

In this project, we worked with a group of stakeholders to refine 29 identified research gaps and transform them into eight highest-priority research needs in the field of ADHD. These highest-level needs included a broad range of issues cutting across age range, key clinical issues, and epidemiological concerns. Within this group of eight, clear themes emerged: the need for improved measurement tools, more generalizable study populations and settings, longer follow-up periods, more understanding of patient-level predictors of response, and more comparative evaluation of psychopharmacologic, psychosocial, and combination interventions across age ranges. PICOTS construction aided our consideration of study design issues and our sample power analyses demonstrated the clear pragmatic barriers that many of the potential designs will present. Advanced secondary data-analysis methods may allow some of these complex questions to be addressed in a more cost-effective manner but will not be able to fully replace the need for new large, long-term trials to evaluate these complex research needs in ADHD.

References

1. Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment (Draft). Rockville, MD: Agency for Healthcare Research and Quality, in press. Available at: http://effectivehealthcare.ahrq.gov/.
2. Miller AR, Lalonde CE, McGrail KM, et al. Prescription of methylphenidate to children and youth, 1990-1996. Cmaj 2001 Nov 27;165(11):1489-94. PMID: 11762572.
3. Robison LM, Sclar DA, Skaer TL, et al. National trends in the prevalence of attention-deficit/hyperactivity disorder and the prescribing of methylphenidate among school-age children: 1990-1995. Clin Pediatr (Phila) 1999 Apr;38(4):209-17. PMID: 10326176.
4. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. Pediatrics 1996 Dec;98(6 Pt 1):1084-8. PMID: 8951257.
5. Brownell MD, Yogendran MS. Attention-deficit hyperactivity disorder in Manitoba children: medical diagnosis and psychostimulant treatment rates. Can J Psychiatry 2001 Apr;46(3):264-72. PMID: 11320681.
6. Rappley MD, Gardiner JC, Jetton JR, et al. The use of methylphenidate in Michigan. Arch Pediatr Adolesc Med 1995 Jun;149(6):675-9. PMID: 7767425.
7. Achenbach TM, Dumenci L, Rescorla LA. Are American children's problems still getting worse? A 23-year comparison. J Abnorm Child Psychol 2003 Feb;31(1):1-11. PMID: 12597695.
8. Charach A, Cao H, Schachar R, et al. Correlates of methylphenidate use in Canadian children: a cross-sectional study. Can J Psychiatry 2006 Jan;51(1):17-26. PMID: 16491980.
9. Zito JM, Safer DJ, Valluri S, et al. Psychotherapeutic medication prevalence in Medicaid-insured preschoolers. J Child Adolesc Psychopharmacol 2007 Apr;17(2):195-203. PMID: 17489714.
10. Pliszka S, AACP Work Group on Quality Issues. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Can Acad Child Adolesc Psychiatry 2007;46(7):894-921. PMID: 17581453.
11. Greenhill LL, Posner K, Vaughan BS, et al. Attention deficit hyperactivity disorder in preschool children. Child Adolesc Psychiatr Clin N Am 2008 Apr;17(2):347-66, ix. PMID: 18295150.
12. Simon V, Czobor P, Balint S, et al. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry 2009 Mar;194(3):204-11. PMID: 19252145.
13. Jadad AR, Boyle M, Cunningham C, et al. Treatment of attention-deficit/hyperactivity disorder. Evid Rep Technol Assess (Summ) 1999 Nov(11):i-viii, 1-341. PMID: 10790990.
14. Murray DW. Treatment of preschoolers with attention-deficit/hyperactivity disorder. Curr Psychiatry Rep 2010 Oct;12(5):374-81. PMID: 20676944.
15. Wilens TE, Faraone SV, Biederman J. Attention-deficit/hyperactivity disorder in adults. JAMA 2004 Aug 4;292(5):619-23. PMID: 15292088.
16. Kooij SJ, Bejerot S, Blackwell A, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC Psychiatry 2010;10:67. PMID: 20815868.
17. Chavez B, Sopko MA, Jr., Ehret MJ, et al. An update on central nervous system stimulant formulations in children and adolescents with attention-deficit/hyperactivity disorder. Ann Pharmacother 2009 Jun;43(6):1084-95. PMID: 19470858.
18. Ipser J, Stein DJ. Systematic review of pharmacotherapy of disruptive behavior disorders in children and adolescents. Psychopharmacology (Berl) 2007 Mar;191(1):127-40. PMID: 16983542.

19. Centers for Disease Control and Prevention (CDC): Mental health in the United States. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder--United States, 2003. Morbidity and Mortality Weekly Report 2005 Sep 2;54(34):842-7. PMID: 16138075.

20. Kratochvil CJ, Greenhill LL, March JS, et al. The role of stimulants in the treatment of preschool children with attention-deficit hyperactivity disorder. CNS drugs 2004;18(14):957-66. PMID: 15584766.

21. Molina BS, Hinshaw SP, Swanson JM, et al. The MTA at 8 years: prospective follow-up of children treated for combined-type ADHD in a multisite study. J Am Acad Child Adolesc Psychiatry 2009 May;48(5):484-500. PMID: 19318991.

22. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. Arch Gen Psychiatry 1999 Dec;56(12):1073-86. PMID: 10591283.

23. Arnold BF, Hogan DR, Colford JM, Jr., et al. Simulation methods to estimate design power: an overview for applied research. BMC Med Res Methodol 2011 Jun 20;11(1):94. PMID: 21689447.

24. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 1971 Dec 23;285(26):1441-6. PMID: 5122894.

25. Curran PJ, Hussong AM, Cai L, et al. Pooling data from multiple longitudinal studies: the role of item response theory in integrative data analysis. Dev Psychol 2008 Mar;44(2):365-80. PMID: 18331129.

Abbreviations

ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AHRQ	Agency for Healthcare Research and Quality
ATX	atomoxetine
CD	Conduct disorder
CE	Comparative Effectiveness Review
CI	confidence interval
DEX	dextroamphetamine
DSM	Diagnostic and Statistical Manual
EHC	Effective Health Care
EPCs	Evidence-based Practice Centers
FRN	Future Research Need
ICTRP	International Clinical Trials Registry Project
KQ	Key Question
MA	mixed amphetamphetamine salts
MIPD	Meta-analysis of Individual Participant Data
MPH	methylphenidate
MTA	Multimodal Treatment Study of Children with Attention Deficit Hyperactivity Disorder
N/A	Not applicable
NCSH	National Survey of Child Health
ODD	Oppositional defiant disorder
PBRNs	practice-based research networks
PICOTs	populations, interventions, comparators, outcomes, timeframes, and settings
RCT	randomized controlled trial
SCHIP	State Children's Health Insurance Program
XR	extended release

Appendix A. Research Gaps Identified From the Draft AHRQ Review: Attention Deficit Hyperactivity Disorder: Effectiveness of Treatment in At-Risk Preschoolers; Long-Term Effectiveness in All Ages; and Variability in Prevalence, Diagnosis, and Treatment

(Draft report posted October 2010)

To generate the list below, content and methodological experts at the RTI-UNC Evidence-based Practice Center (EPC) reviewed the draft review and produced a list of evidence gaps from the limitations and recommendations for future research sections in the report. The list was supplemented by identifying gaps mentioned in the report text that were not explicitly described in either of these sections. We wished to be inclusive at this stage of the future research needs process, providing the stakeholders with the full range of evidence gaps identified throughout the report. Minor rewording of the evidence gaps in the EPC report was conducted for consistency. The list below is in no particular order; the numbers are for reference only.

Preliminary list of evidence gaps from the draft review

Gap #	Evidence Gap
1	Limited data are available about the relative efficacy of psychosocial and behavioral treatment programs (e.g., parent training compared with summer behavior treatment programs) for children less than 6 years of age with disruptive behavior disorder or ADHD. (KQ 1)
2	Limited data are available about the relative efficacy of psychosocial and behavioral treatment programs (e.g., parent training compared with summer behavior treatment programs) for children ages 6 years or older with or ADHD. (KQ 2)
3	There is a paucity of research among children less than 6 years of age with disruptive behavior disorder or ADHD examining positive child treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based interventions, or other cross-sectorial evaluations), and effects on specific subgroups. (KQ 1)
4	There is a paucity of research among children ages 6 years or older with ADHD examining positive child treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based intervention), and effects on specific subgroups. (KQ 2)
5	There are few efficacy studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components for preschoolers with disruptive behavior disorder or ADHD based on the child's needs. (KQ 1)
6	There are few efficacy studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components for children ages 6 years and older with ADHD based on the child's needs. (KQ 2)
7	There is a paucity of studies among children less than 6 years of age with disruptive behavior disorder or ADHD documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions. (KQ 1)
8	There is a paucity of studies among children ages 6 years of age or older with ADHD documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions. (KQ 2)
9	There are limited data on the influence of parental preferences regarding treatment approaches or modes of service delivery on short- and long-term outcomes for children less than 6 years of age. (KQ 1)
10	There is a paucity of studies among children less than 6 years of age with disruptive behavior disorder or ADHD that disassemble the key components of available psychosocial and behavioral treatment programs (e.g., specific parent training techniques compared to treatment components targeting the child and variants in service delivery to accommodate parental preferences). (KQ 1)

Gap #	Evidence Gap
11	Conflicting results from treatment studies of children less than 6 years of age with disruptive behavior disorder or ADHD show improvements in ADHD symptoms when the parent behavior training protocol is adjusted and when the protocol is not adjusted. Studies comparing the relative efficacy among children less than 6 years of age with disruptive behavior disorder or ADHD of specific adjustments to parent behavior training protocols are currently not available. (KQ 1)
12	There are limited data available from studies with appropriate comparison groups about long-term outcomes for preschool interventions. (KQ 1)
13	For people ages 6 years or older with ADHD, there are limited data available examining longer-term follow-up of psychosocial and pharmacological ADHD treatments with appropriate comparison groups for long-term outcomes including academic and educational outcomes. (KQ 2)
14	There is a paucity of prospective combination pharmacological studies (e.g., combination pharmacotherapy treatment in ADHD [stimulants + antipsychotics, stimulants + alpha agents]) among people ages 6 years or older with ADHD as well as studies that follow individuals no longer requiring medication. (KQ 2)
15	There is a paucity of studies among people with ADHD ages 6 years or older that examine mediators and moderators of positive treatment response. The extant literature provides limited information about variations in treatment response by specific sociodemographic characteristics (e.g., low socioeconomic status, gender, different racial or ethnic groups) and baseline clinical indices (e.g., comorbidity with other psychiatric disorders, ADHD subtypes, comorbid developmental disorders, comorbid learning disabilities, language impairments, reading or mathematics disorders). (KQ 2)
16	Standardized outcome measures such as global impairment scales or quality of life scales are needed to compare study outcomes from different cohorts of people with ADHD ages 6 years and older. (KQ 2)
17	Research among people with ADHD ages 6 years and older that compares efficacy as measured by different data-capturing methods such as child self-rating scales, parent rating scales, and semistructured interviews is limited. (KQ 2)
18	There is limited research on the impact of discrepancies between multiple informants (e.g., parent vs. child; parent vs. teacher; parent vs. clinician) on the effectiveness of treatments for people of all ages with ADHD. (KQ 2, 3)
19	The extant literature lacks evidence-based performance measures for assessing prevalence and treatment outcomes for people of all ages with ADHD on a comparable metric. Standardized methods of data collection, case identification, and outcomes measurement in epidemiologic surveys and administrative databases are lacking, particularly for adolescents and adults. (KQ 3)
20	Beyond randomized controlled trial protocols, there is limited research that examines patterns of service usage and factors that influence access and receipt of health services such as cross-sector coordination of health services, family and child factors, and availability of health insurance for people of all ages with ADHD. (KQ 3)

Appendix B. Web-Based Prioritization Exercises

Figure B-1. Prioritization Exercise #1

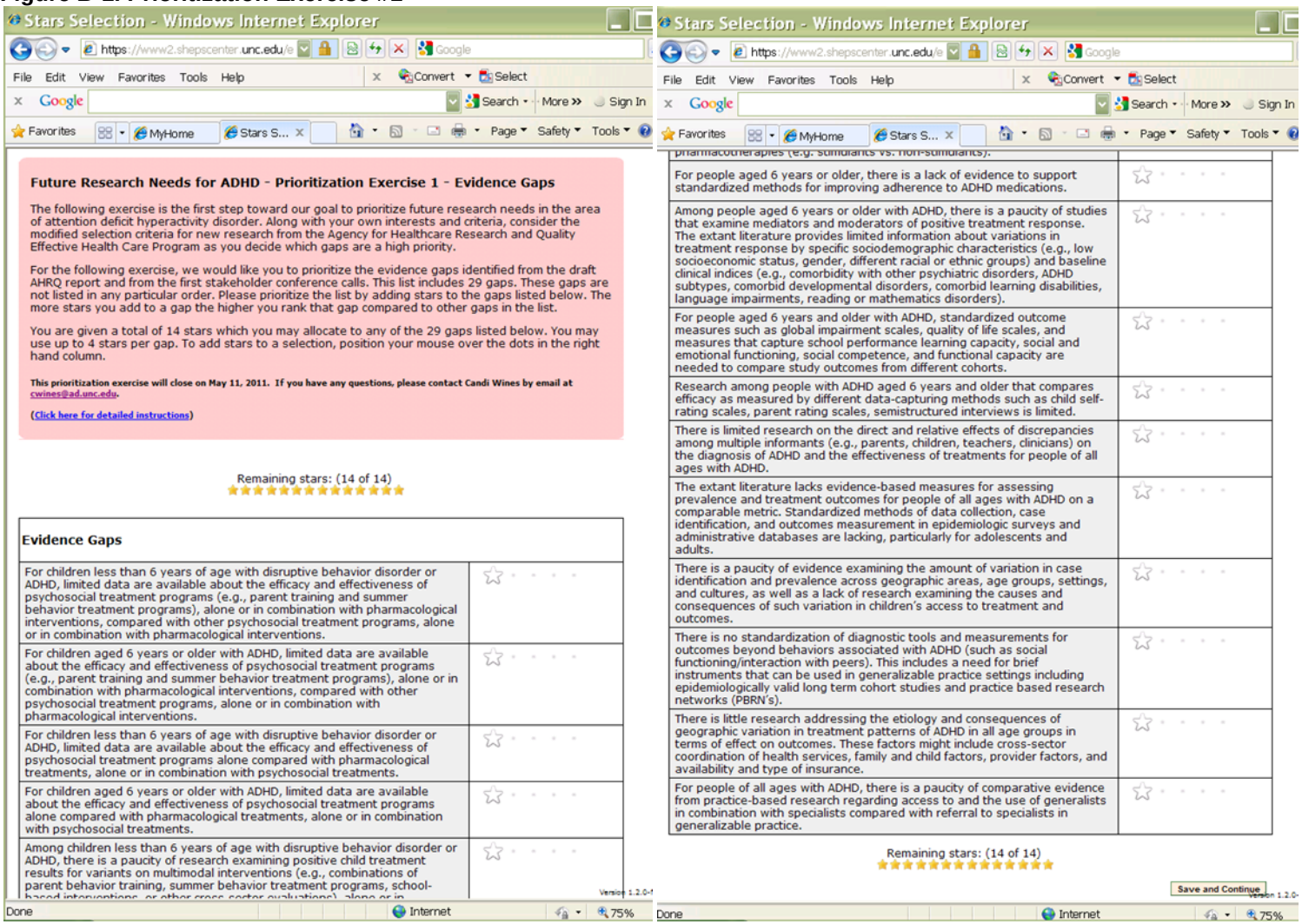
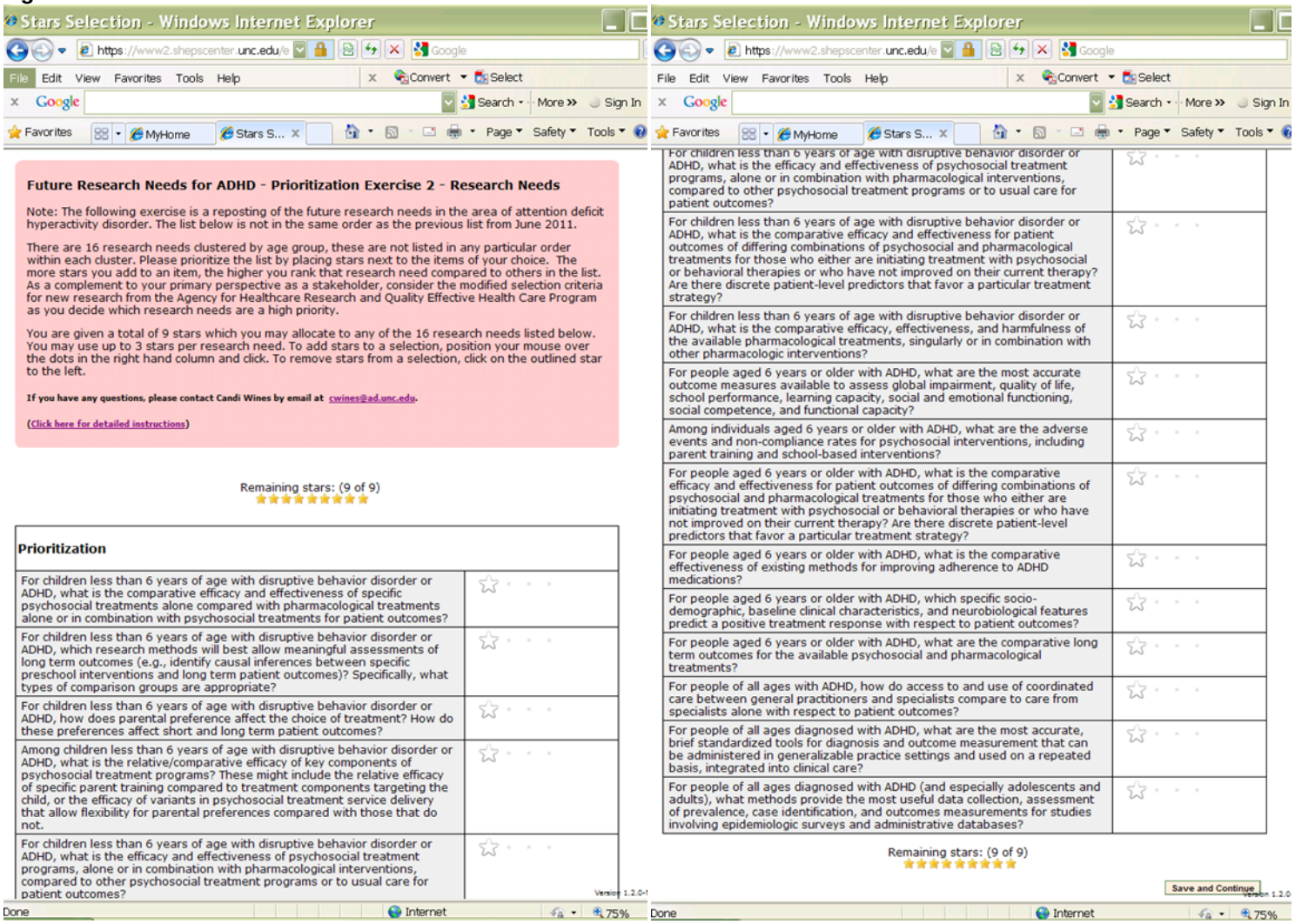


Figure B-2. Prioritization exercise #2



Appendix C. Effective Health Care (EHC) Program Selection Criteria (Modified To Emphasize the Three Elements Most Applicable to Stakeholders Considering Future Research Needs on a Topic Already Under Review by the EHC)

- Importance
  - Represents a significant disease burden, large proportion, or priority population
  - Is of high public interest; affects health care decisionmaking, outcomes, or costs for a large proportion of the U.S. population or for a priority population in particular
  - Represent important uncertainty for decisionmakers
  - Incorporates issues around both clinical benefits and potential clinical harms
  - Represents important variation in clinical care, or controversy in what constitutes appropriate clinical care
  - Represent high costs due to common use, to high unit costs, or to high associated costs to consumers, to patients, to health care systems, or to payers
- Desirability of new research/duplication
  - Would not be redundant (the proposed gaps have not been sufficiently addressed by previous research)
- Potential Impact
  - Potential for significant health impact, significant economic impact, potential change, potential risk from inaction, addressing inequities and vulnerable populations, and/or addressing a topic with clear implications for resolving important dilemmas in health and health care decisions made by one or more stakeholder groups

Appendix D. ADHD (FRN) Searches for Ongoing Research

VERSION 3—more focused searches, January 18, 2011, limiting to March 2008 (or 2008 where month limit not possible); and a smaller number of terms.

I. RePORTER—limited to Active Projects and Award Notice Date greater than February 28, 2008.

"attention deficit,adhd"

= 347 results (saved as .csv/Excel files)

II. HSRProj—using the same search as before, and limiting Initial Year range 2008-2011

aggression OR "aggressive behavior" OR aggressiveness OR "agonistic behavior" OR anger OR "attention deficit" OR "attention span" OR addh OR adhd OR "attention deficit and disruptive behavior disorders" OR "attention deficit disorder with hyperactivity" OR "behavior disorder" OR "behavior problems" OR bullying OR "Child Behavior Disorders" OR "conduct disorder" OR "disruptive behavior" OR "disruptive disorder" OR distractability OR hostility OR hyperactive OR hyperactivity OR hyperkinesia OR Hyperkinesis OR hyperkinetic OR "Impulse Control Disorders" OR "Impulsive Behavior" OR impulsiveness OR inattention OR inattentive OR "minimal brain dysfunction" OR "oppositional defiant disorder" OR "self control"

= 57 results. Imported to EndNote, file name = ADHD-HSRProj_v.3(57).enl

III. ClinicalTrials.gov—same strategy as with RePORTER. In advanced search screen, limited to First Received: From 03/01/2008 To 01/18/2011.

"attention deficit" OR adhd

= 260 studies. saved as a zip (text) file, filename = CT.govADHDv.3(260).zip

IV. ICTRP (International Clinical Trials Registry Platform) test search strategy and URL sent to Candi Wines and Dan Jonas on 1/18 for them to evaluate the usefulness of the results. Same search strategy as with RePORTER and CT.gov:

Advanced Search screen:
http://apps.who.int/trialsearch/AdvSearch.aspx

Search in Condition box:
"attention deficit" OR adhd

Fill in Date of registration between: 03/01/2008 and 01/18/2011

= 124 records for 122 trials found (copied and pasted the text from each record into a Word document)

If the same search is repeated, only moving the search terms to the Title search box, 97 records for 97 trials are found.

Of those, 13 were not in the original search (determined by whether or not the link was blue [unviewed] or purple [viewed])), and all look possibly relevant, so these were appended to the first search.

There was a problem with the results: there were actually between 300-400 results returned, more than the database reported at the conclusion of the query. The librarian copied and saved 155 records in full format. She also created a list of all results in case reviewers would like to see more; the librarian noticed that many of the results were not on topic and also did not contain either of the search terms. Once she noticed that she had saved some irrelevant records, of those remaining on pages 3-4 (records were displayed 100 per page) she only saved records that referred to ADHD or "attention deficit" in the title, but did not notice this database error in time to avoid copying some that were not relevant. Specifically:

#1-#100 look relevant

#101 is Early Diagnosis and Stem Cell Transplantation for Severe Immunodeficiency Diseases SIDS
#102 is Effect of Vitamin D Treatment in Primary Hyperparathyroidism
#103 is Evaluation of the Effect of Bezafibrate on Muscle Metabolism During Exercise in Patients With CPTII and VLCAD Deficiency
#104 is Effect of Diet-induced Weight Loss on HIV-associated Metabolic Syndrome
#105 is Effect of vitamin D on the systolic blood pressure in hypertensive patients with low vitamin D levels.
#106 is Effect of Vitamin D Replacement During Winter Months in Patients With Hypertension
#107 is Effect of Vitamin D3 on Vascular Function
#108 is Acute effects of growth hormone on cognitive functioning and related brain physiology in healthy subjects.
#109 is relevant
#110 is Effectiveness of generic split adult tablets and paediatric fixed dose combination (FDC) of d4T/3TC/NVP in the treatment of HIV infected Malawian children TrioPed
#111 is relevant
#112 is Effects of a supervised exercise program on the physical fitness, immunological function and quality of life of Human immunodeficiency virus (HIV)-Infected Patients.
#113 is relevant
#114 is Effects of Dietary Heme/Non-heme Iron and Helicobacter Pylori (Hp) Infection on Maternal Iron-deficiency Anemia and Fetal Growth Outcomes
#115 is Effects of Vitamin D Supplement Before and During Pregnancy on Birth Weight Gravita
#116 is Effects of Vitamin D Supplementation in Coronary Artery Disease-patients With Postchallenge Hyperglycemia and Vitamin D Deficiency
#117 is Effects of Vitamin D Supplementation in Obesity

#118 is Efficacy and Safety of GSK Biologicals HIV Vaccine in Antiretroviral Therapy (ART)-naïve HIV-1 Infected Persons
#119 is Efficacy and Safety of Intravenous Ferric Carboxymaltose (FCM) in Patients With Iron Deficiency Anemia (IDA)
#120 is Efficacy and Safety of Prothromplex Total (Prothrombin Complex Concentrate) in Oral Anticoagulant Reversal
#121 is Efficacy and safety of strontium ranelate/vitamin D3 combination on vitamin D deficiency in the treatment of osteoporotic patient N/A
#122 is Efficacy of Cultivated Corneal Epithelial Stem Cell for Ocular Surface Reconstruction
#123 is Efficacy of Daily Vitamin D3 Supplementation in Normal Weight Adolescents
#124 is Efficacy of Double Fortified Salt (DFS) to Improve Work Productivity in Women in India DFS #125 is Efficacy of Thrice Weekly Intermittent Short Course Antituberculosis Chemotherapy in Tuberculosis Patients With and Without HIV Infection
#126 is Epidemiological studies for clinical manifestations and case numbers of inborn errors of ketone body metabolism
#127 is Epigenetic Markers of B-Cell Function in Low Birth Weight Infants
#128 is Establishing Fibroblast-derived Cell Lines From Skin Biopsies of Patients With Immunodeficiency or Immunodysregulation Disorders
#129 is about HIV Tx
#130 is about CVD/HIV
#131 is about COPD
#132-133 are about treating iron deficiency
#134 is about muscular dystrophy

#135-155 look relevant.

UNDUPLICATED TOTAL WITHOUT ICTRP RESULTS: 664

UNDUPLICATED TOTAL INCLUDING ICTRP RESULTS: 819

VERSION 2—December 22, 2010 revision (limiting to award or start date from the last 5 years, Humans and English when possible):

I. RePORTER (limited to Active Projects and Award Notice Date greater than January 1, 2006; no limits available for Humans and English):

“LARGE” search, inclusive of all ADHD and related terms used by McMaster

“aggression,aggressive behavior,aggressiveness,agonistic behavior,anger,attention deficit,attention span,addh,adhd,attention deficit and disruptive behavior disorders,attention deficit disorder with hyperactivity,behavior disorder,behavior problems,bullying,Child Behavior Disorders,conduct disorder,disruptive behavior,disruptive disorder,distractability,hostility,hyperactive,hyperactivity,hyperkinesia,Hyperkinesis,hyperkinetic,Impulse Control Disorders,Impulsive Behavior,impulsiveness,inattention,inattentive,minimal brain dysfunction,oppositional defiant disorder,self control”

Still too large at 1864. Not saved.

“MEDIUM” Selected more specific ADHD and related terms

“attention deficit,attention span,addh,adhd,attention deficit and disruptive behavior disorders,attention deficit disorder with hyperactivity,behavior disorder,behavior problems,Child Behavior Disorders,disruptive behavior,disruptive disorder,distractability,hyperactive,hyperactivity,hyperkinesia,Hyperkinesis,hyperkinetic,Impulse Control Disorders,Impulsive Behavior,impulsiveness,inattention,inattentive,minimal brain dysfunction,oppositional defiant disorder”

=1142 results, not saved

“FOCUSED” Results only about AHDH:

“attention deficit,attention span,addh,adhd,attention deficit and disruptive behavior disorders,attention deficit disorder with hyperactivity,child behavior disorders”

=590 results—downloaded 100 or fewer per file, so that abstracts are included when present. For download files larger than 100 records, abstracts are not included. There will also be some duplicates in the files, because RePORTER creates on-the-fly search results from a relational database. If a project has more than one funding agency contributing, the project is listed for each funder. This is the least user-friendly of the three databases searched.

II. HSRProj focused search

This search was left broad because the focus of the database is Health Services Research and Public health, and the size of the database is small, so we want to search it more thoroughly using all terms employed by the McMaster team. So the original search from Dec. 20 was kept:

aggression OR “aggressive behavior” OR aggressiveness OR “agonistic behavior” OR anger OR “attention deficit” OR “attention span” OR addh OR adhd OR “attention deficit and disruptive behavior disorders” OR “attention deficit disorder with hyperactivity” OR “behavior disorder” OR “behavior problems” OR bullying OR “Child Behavior Disorders” OR “conduct disorder” OR “disruptive behavior” OR “disruptive disorder” OR distractability OR hostility OR hyperactive OR hyperactivity OR hyperkinesia OR Hyperkinesis OR hyperkinetic OR “Impulse Control Disorders” OR “Impulsive Behavior” OR impulsiveness OR inattention OR inattentive OR “minimal brain dysfunction” OR “oppositional defiant disorder” OR “self control”

=199 projects saved in an EndNote library 12/20/2010

III. ClinicalTrials.gov

Expert Search of all fields:

Full “LARGE” search was completed and limited to studies First Received between 01/01/2006-12/22/2010:

(aggression OR “aggressive behavior” OR aggressiveness OR “agonistic behavior” OR anger OR “attention deficit” OR “attention span” OR addh OR adhd OR “attention deficit and disruptive behavior disorders” OR “attention deficit disorder with hyperactivity” OR “behavior disorder” OR “behavior problems” OR bullying OR “Child Behavior Disorders” OR “conduct disorder” OR “disruptive behavior” OR “disruptive disorder” OR distractability OR hostility OR hyperactive OR hyperactivity OR hyperkinesia OR Hyperkinesis OR hyperkinetic OR “Impulse Control Disorders” OR “Impulsive Behavior” OR impulsiveness OR inattention OR inattentive OR “minimal brain dysfunction” OR “oppositional defiant disorder” OR “self control”) [DISEASE] AND (“01/01/2006” : “12/22/2010”) [FIRST-RECEIVED-DATE]

=786 studies, not saved

“MEDIUM” search was completed and limited to studies First Received between 01/01/2006-12/22/2010:

(“attention deficit” OR “attention span” OR addh OR adhd OR “attention deficit and disruptive behavior disorders” OR “attention deficit disorder with hyperactivity” OR “behavior disorder” OR “behavior problems” OR “Child Behavior Disorders” OR “disruptive behavior” OR “disruptive disorder” OR distractability OR hyperactive OR hyperactivity OR hyperkinesia OR Hyperkinesis OR hyperkinetic OR “Impulse Control Disorders” OR “Impulsive Behavior” OR impulsiveness OR inattention OR inattentive OR “minimal brain dysfunction” OR “oppositional defiant disorder”) [DISEASE] AND (“01/01/2006” : “12/22/2010”) [FIRST-RECEIVED-DATE]

= 611 studies, not saved

“FOCUSED” Results only about AHDH:

“attention deficit” OR “attention span” OR addh OR adhd OR “attention deficit and disruptive behavior disorders” OR “attention deficit disorder with hyperactivity” OR “child behavior disorders”

= 391 studies—saved as a zip (text) file

VERSION 1—(Dec. 20, 2010)—Original Searches

I. ADHD search strings for RePORTER:

“LARGE” search, inclusive of all ADHD terms used by McMaster

“aggression,aggressive behavior,aggressiveness,agonistic behavior,anger,attention deficit,attention span,addh,adhd,attention deficit and disruptive behavior disorders,attention deficit disorder with hyperactivity,behavior disorder,behavior problems,bullying,Child Behavior

Disorders,conduct disorder,disruptive behavior,disruptive disorder,distractability,hostility,hyperactive,hyperactivity,hyperkinesia,Hyperkinesis,hyperkinetic,Impulse Control Disorders,Impulsive Behavior,impulsiveness,inattention,inattentive,minimal brain dysfunction,oppositional defiant disorder,self control"

=2392 results, not saved

"MEDIUM" Selected more specific ADHD terms

"attention deficit,attention span,addh,adhd,attention deficit and disruptive behavior disorders,attention deficit disorder with hyperactivity,behavior disorder,behavior problems,Child Behavior Disorders,disruptive behavior,disruptive disorder,distractability,hyperactive,hyperactivity,hyperkinesia,Hyperkinesis,hyperkinetic,Impulse Control Disorders,Impulsive Behavior,impulsiveness,inattention,inattentive,minimal brain dysfunction,oppositional defiant disorder"

=1487 results, not saved

"FOCUSED" Results only about AHDH:

"attention deficit,attention span,addh,adhd,attention deficit and disruptive behavior disorders,attention deficit disorder with hyperactivity"

=759 results—downloaded 100 per file, so that abstracts are included when present. For download files larger than 100 records, there are no abstracts included. This is the least "user-friendly" of the three databases searched.

II. ADHD search for HSRProj:

aggression OR "aggressive behavior" OR aggressiveness OR "agonistic behavior" OR anger OR "attention deficit" OR "attention span" OR addh OR adhd OR "attention deficit and disruptive behavior disorders" OR "attention deficit disorder with hyperactivity" OR "behavior disorder" OR "behavior problems" OR bullying OR "Child Behavior Disorders" OR "conduct disorder" OR "disruptive behavior" OR "disruptive disorder" OR distractability OR hostility OR hyperactive OR hyperactivity OR hyperkinesia OR Hyperkinesis OR hyperkinetic OR "Impulse Control Disorders" OR "Impulsive Behavior" OR impulsiveness OR inattention OR inattentive OR "minimal brain dysfunction" OR "oppositional defiant disorder" OR "self control"

=199 projects saved in an EndNote library, kept

III. ClinicalTrials.gov

Expert Search of all fields:

Full "LARGE" search:

aggression OR “aggressive behavior” OR aggressiveness OR “agonistic behavior” OR anger OR “attention deficit” OR “attention span” OR addh OR adhd OR “attention deficit and disruptive behavior disorders” OR “attention deficit disorder with hyperactivity” OR “behavior disorder” OR “behavior problems” OR bullying OR “Child Behavior Disorders” OR “conduct disorder” OR “disruptive behavior” OR “disruptive disorder” OR distractability OR hostility OR hyperactive OR hyperactivity OR hyperkinesia OR Hyperkinesis OR hyperkinetic OR “Impulse Control Disorders” OR “Impulsive Behavior” OR impulsiveness OR inattention OR inattentive OR “minimal brain dysfunction” OR “oppositional defiant disorder” OR “self control”

=2463 studies, not saved

“FOCUSED” Results only about AHDH:

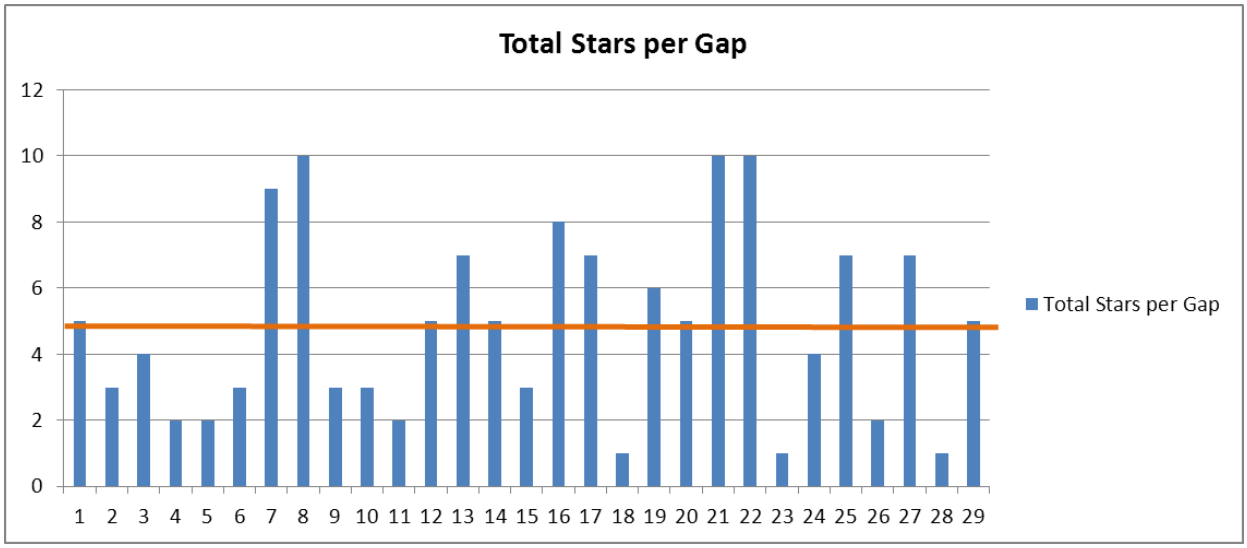
“attention deficit” OR “attention span” OR addh OR adhd OR “attention deficit and disruptive behavior disorders” OR “attention deficit disorder with hyperactivity”

= 582 studies—saved as a zip (text) file—later discarded

Appendix E. FRN-ADHD Evidence Gaps Prioritization Exercise

Results

Total Stars Allotted to Each Gap (N = 10 responders)



Orange line shows cut off between Upper Tier and Lower Tier.

Ranked List of Evidence Gaps after 1st Round of Prioritization

Upper Tier Evidence Gaps (Those Receiving 5 or More Stars)

Variable Code	Evidence Gap Text	# Stars	# People
EG8	For people ages 6 years or older with ADHD, there are few efficacy and effectiveness studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components based on the person's needs.	10	6
EG21	Among people ages 6 years or older with ADHD, there is a paucity of studies that examine mediators and moderators of positive treatment response. The extant literature provides limited information about variations in treatment response by specific sociodemographic characteristics (e.g., low socioeconomic status, gender, different racial or ethnic groups) and baseline clinical indices (e.g., comorbidity with other psychiatric disorders, ADHD subtypes, comorbid developmental disorders, comorbid learning disabilities, language impairments, reading or mathematics disorders).	10	7
EG22	For people ages 6 years and older with ADHD, standardized outcome measures such as global impairment scales, quality of life scales, and measures that capture school performance learning capacity, social and emotional functioning, social competence, and functional capacity are needed to compare study outcomes from different cohorts.	10	6
EG7	For preschoolers with disruptive behavior disorder or ADHD, there are few efficacy and effectiveness studies on prescriptive treatments or optimal circumstances for adding specific psychosocial and/or pharmacological treatment components based on the child's needs.	9	6

Variable Code	Evidence Gap Text	# Stars	# People
EG16	There are limited data available from studies with appropriate comparison groups about long-term outcomes for preschool interventions.	8	6
EG13	For children less than 6 years of age with ADHD, there are limited data on the influence of parental preferences regarding treatment approaches or modes of service delivery on short- and long-term outcomes.	7	4
EG17	For people ages 6 years or older with ADHD, there are limited data available examining longer term follow-up of psychosocial and pharmacological ADHD treatments with appropriate comparison groups for long-term outcomes including academic and educational outcomes.	7	5
EG25	The extant literature lacks evidence-based measures for assessing prevalence and treatment outcomes for people of all ages with ADHD on a comparable metric. Standardized methods of data collection, case identification, and outcomes measurement in epidemiologic surveys and administrative databases are lacking, particularly for adolescents and adults.	7	5
EG27	There is no standardization of diagnostic tools and measurements for outcomes beyond behaviors associated with ADHD (such as social functioning/interaction with peers). This includes a need for brief instruments that can be used in generalizable practice settings including epidemiologically valid long-term cohort studies and practice-based research networks (PBRNs).	7	5
EG19	Among children less than 6 years of age with ADHD, there is a paucity of prospective studies that compare the efficacy, effectiveness, and harms of single and/or combination pharmacotherapies with other single or combined pharmacotherapies (e.g., stimulants vs. nonstimulants).	6	3
EG1	For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions.	5	4
EG12	Among individuals ages 6 years or older with ADHD, there is a paucity of studies documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions.	5	4
EG14	Among children less than 6 years of age with disruptive behavior disorder or ADHD, there is a paucity of studies that disassemble the key components of available psychosocial treatment programs (e.g., specific parent training techniques compared to treatment components targeting the child and variants in service delivery to accommodate parental preferences).	5	4
EG20	For people ages 6 years or older, there is a lack of evidence to support standardized methods for improving adherence to ADHD medications.	5	3
EG29	For people of all ages with ADHD, there is a paucity of comparative evidence from practice-based research regarding access to and the use of generalists in combination with specialists compared with referral to specialists in generalizable practice.	5	4

Lower Tier Evidence Gaps (Those Receiving 4 or Fewer Stars)

Variable Code	Evidence Gap Text	# Stars	# People
EG3*	For children less than 6 years of age with disruptive behavior disorder or ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs alone compared with pharmacological treatments, alone or in combination with psychosocial treatments.	4	3
EG24	There is limited research on the direct and relative effects of discrepancies among multiple informants (e.g., parents, children, teachers, clinicians) on the diagnosis of ADHD and the effectiveness of treatments for people of all ages with ADHD.	4	2

Variable Code	Evidence Gap Text	# Stars	# People
EG2	For children ages 6 years or older with ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs (e.g., parent training and summer behavior treatment programs), alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs, alone or in combination with pharmacological interventions.	3	2
EG6	Among children ages 6 years or older with ADHD, there is a paucity of research examining positive treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based intervention) alone or in combination with pharmacological interventions, and effects on specific subgroups.	3	2
EG9	Among people ages 6 years or older with ADHD, there is a lack of high-quality studies on the efficacy and effectiveness of biofeedback and working memory training.	3	2
EG10	Among people less than 6 years of age with disruptive behavior disorder or ADHD, there is a lack of high-quality studies on the efficacy and effectiveness of biofeedback and working memory training.	3	2
EG15	Conflicting results from treatment studies of children less than 6 years of age with disruptive behavior disorder or ADHD show improvements in ADHD symptoms when the parent behavior training protocol is flexible and when the protocol is not flexible. Among children less than 6 years of age with disruptive behavior disorder or ADHD, studies comparing the relative efficacy of flexible versus nonflexible parent behavior training protocols are currently not available.	3	2
EG4	For children ages 6 years or older with ADHD, limited data are available about the efficacy and effectiveness of psychosocial treatment programs alone compared with pharmacological treatments, alone or in combination with psychosocial treatments.	2	1
EG5	Among children less than 6 years of age with disruptive behavior disorder or ADHD, there is a paucity of research examining positive child treatment results for variants on multimodal interventions (e.g., combinations of parent behavior training, summer behavior treatment programs, school-based interventions, or other cross-sector evaluations), alone or in combination with pharmacological interventions, and effects on specific subgroups.	2	1
EG11	Among children ages less than 6 years with disruptive behavior disorder or ADHD, there is a paucity of studies documenting adverse events or noncompliance rates for psychosocial interventions including parent training and school-based interventions.	2	2
EG26	There is a paucity of evidence examining the amount of variation in case identification and prevalence across geographic areas, age groups, settings, and cultures, as well as a lack of research examining the causes and consequences of such variation in children's access to treatment and outcomes.	2	2
EG18	Among people ages 6 years or older with ADHD, there is a paucity of prospective combination pharmacological studies (e.g., combination pharmacotherapy treatment) as well as studies that follow individuals no longer requiring medication.	1	1
EG23	Research among people with ADHD ages 6 years and older that compares efficacy as measured by different data-capturing methods such as child self-rating scales, parent rating scales, semistructured interviews is limited.	1	1
EG28	There is little research addressing the etiology and consequences of geographic variation in treatment patterns of ADHD in all age groups in terms of effect on outcomes. These factors might include cross-sector coordination of health services, family and child factors, provider factors, and availability and type of insurance.	1	1

*EG3 was moved to the upper tier at the request of the stakeholders.

Appendix F. FRN-ADHD Research Needs

Developed From the Upper Tier Evidence Gaps (N = 16)

Numbers are for reference only and do not represent any particular order.

Research Needs for Those Less Than 6 Years of Age

For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness of specific psychosocial treatments alone compared with pharmacological treatments alone or in combination with psychosocial treatments for patient outcomes*?

For children less than 6 years of age with disruptive behavior disorder or ADHD, which research methods will best allow meaningful assessments of long-term outcomes (e.g., identify causal inferences between specific preschool interventions and long-term patient outcomes*)? Specifically, what types of comparison groups are appropriate?

For children less than 6 years of age with disruptive behavior disorder or ADHD, how does parental preference affect the choice of treatment? How do these preferences affect short and long-term patient outcomes*?

Among children less than 6 years of age with disruptive behavior disorder or ADHD, what is the relative/comparative efficacy of key components of psychosocial treatment programs? These might include the relative efficacy of specific parent training compared with treatment components targeting the child, or the efficacy of variants in psychosocial treatment service delivery that allow flexibility for parental preferences compared with those that do not.

For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the efficacy and effectiveness of psychosocial treatment programs, alone or in combination with pharmacological interventions, compared with other psychosocial treatment programs or to usual care for patient outcomes*?

For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy and effectiveness for patient outcomes* of differing combinations of psychosocial and pharmacological treatments for those who either are **initiating treatment** with psychosocial or behavioral therapies *or* who have **not improved on their current therapy**? Are there discrete patient-level predictors that favor a particular treatment strategy?

For children less than 6 years of age with disruptive behavior disorder or ADHD, what is the comparative efficacy, effectiveness, and harmfulness of the available pharmacological treatments, singularly or in combination with other pharmacologic interventions?

Research Needs for Those 6 Years of Age or Older

For people ages 6 years or older with ADHD, what are the most accurate outcome measures available to assess global impairment, quality of life, school performance, learning capacity, social and emotional functioning, social competence, and functional capacity?

Among individuals ages 6 years or older with ADHD, what are the adverse events and noncompliance rates for psychosocial interventions, including parent training and school-based interventions?

For people ages 6 years or older with ADHD, what is the comparative efficacy and effectiveness for patient outcomes* of differing combinations of psychosocial and pharmacological treatments for those who either are **initiating treatment** with psychosocial or

behavioral therapies *or* who have **not improved on their current therapy**? Are there discrete patient-level predictors that favor a particular treatment strategy?

For people ages 6 years or older with ADHD, what is the comparative effectiveness of existing methods for improving adherence to ADHD medications?

For people ages 6 years or older with ADHD, which specific sociodemographic, baseline clinical characteristics,^ and neurobiological features‡ predict a positive treatment response with respect to patient outcomes*?

For people ages 6 years or older with ADHD, what are the comparative long-term outcomes+ for the available psychosocial and pharmacological treatments?

Research Needs for People of All Ages

For people of all ages with ADHD, how do access to and use of coordinated care between general practitioners and specialists compare with care from specialists alone with respect to patient outcomes*?

For people of all ages diagnosed with ADHD, what are the most accurate, brief standardized tools for diagnosis and outcome measurement that can be administered in generalizable practice settings and used on a repeated basis, integrated into clinical care?

For people of all ages diagnosed with ADHD (and especially adolescents and adults), what methods provide the most useful data collection, assessment of prevalence, case identification, and outcomes measurements for studies involving epidemiologic surveys and administrative databases?

* Patient outcomes include: change in ADHD symptoms, behavior problems, social functioning, emotional regulation, executive functioning, treatment adherence, global functioning, academics, and parent competence.

^ Sociodemographic and baseline clinical characteristics include: sex, socioeconomic status, race, comorbidity with other psychiatric disorders, ADHD subtypes, comorbid developmental disorders, comorbid learning disabilities, language impairments, reading or mathematics disorders.

‡ Neurobiological features include: genetic variants and neuroimaging abnormalities.

+ Long-term outcomes include educational measures, which encompass academic outcomes.