ECHO Autism
Study Protocol

Version Date: October 25, 2016
Version Number: 3

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PROTOCOL SYNOPSIS

Study Title

ECHO Autism

Version Number

3

Rationale for the Study

ASD is associated with significant impairments in social, communication and behavioral domains and medical and psychiatric comorbidities [1-3]. Unmanaged comorbid conditions contribute to increased stress and burden for families [4-5]. Children with ASD have increased risk for unmet healthcare needs, which is exacerbated among underserved populations [6-8]. Individuals in rural areas face socioeconomic and geographic barriers to accessing health care, including high rates of poverty [9]. They are more likely to lack health Insurance [10]. Rural areas have significant shortages of specialists, necessitating long distance travel for families to access services [10]. Rural children have higher rates of unmet medical and dental needs and of emergency department visits than do non-rural populations [11].

With increasing prevalence of ASD, diagnostic and treatment demands far exceed the capacity of specialty centers [12]. Early identification, referral and effective treatment are essential for enhancing outcomes, yet children with ASD face delays in diagnosis [13]. Although PCPs provide immediate and community-based care for children, they often feel ill-equipped to care for children with ASD [14-15]. Children with ASD experience co-occurring conditions that PCPs could manage, most notably sleep problems and constipation [3, 16-17]. However, PCPs report lack of knowledge and confidence in treating children with ASD, with resulting unmet healthcare needs [14-15]. PCPs also may lack the knowledge to manage ongoing psychotropic medication use. Lack of PCP comfort caring for children with ASD likely contributes to higher rates and duration of hospitalizations, greater expenditures, and greater use of psychotropic medications in children with ASD [18-21]. Thus, there is a critical need to improve early identification of ASD by PCPs and to enhance PCP effectiveness in managing sleep, constipation, psychotropic medications and other co-morbidities for children with ASD.

Study Design

A cluster-randomized design will be used, with sequential, staggered roll-out of the ECHO Autism intervention to 5 clusters of participants over a 1 year period. This design was chosen to maximize our ability to determine effectiveness of the intervention while minimizing potential contamination across groups and addressing potential ethical concerns. First, it would be problematic to randomize at the level of individual participants due to potential contamination across groups. Second, the staggered roll-out allows for comparison of each cluster to contemporaneous control groups as well as to its own baseline. Lastly, there will be a large benefit from the intervention for the participants themselves and we expect a large benefit for the patient populations that they serve as well. Moreover, for the actual participants (PCPs) there is no potential harm (as they receive CME credits for participation). Therefore, randomization of participants to never receiving the intervention would be inappropriate. To enable a rigorous assessment of the effect of the ECHO intervention, we are randomizing different centers (and the participants linked to each center) to starting at different times during the study and will be using multiple data collection points under baseline, ECHO and follow-up conditions.

Study Objectives and Endpoints

Primary Objective: To determine whether participation in a collaborative telehealth intervention will result in improved learning, clinical practice behavior and efficacy among primary care providers (PCPs).

> **Hypothesis 1**: Following participation in ECHO Autism, PCPs will demonstrate significant improvements in ASD knowledge as assessed by pre- to post-intervention knowledge tests in ASD screening and identification and assessment and treatment of medical co-morbidities;

Hypothesis 2: Following participation in ECHO Autism, PCPs will demonstrate significant improvements in clinical practice/behavior as assessed by pre- to post-intervention chart reviews in ASD screening (co-primary outcome) and treatment of medical co-morbidities, in particular, sleep problems and constipation (co-primary outcome).

Hypothesis 3: Following participation in ECHO Autism, PCPs will demonstrate significant improvements in self-efficacy in ASD screening and identification and treatment of medical co-morbidities.

Intervention and Duration

As noted above, a cluster-randomized design will be used, with sequential, staggered roll-out of the ECHO Autism intervention to 5 clusters over a 1 year period. The intervention will be delivered at 10 ECHO Autism Hubs, which will be randomly assigned to one of 5 clusters. Cluster assignment will determine the timing of the intervention start-date for each ECHO Autism Hub. Each ECHO Autism Hub will deliver the intervention to 15 PCP participants (for a total of 150 participants).

Each ECHO Autism Hub will be comprised of a team of up to 5 autism specialists (Physician/Autism Medical Specialist, Psychologist, Family Navigator, Dietician, and Parent Expert). The ECHO Autism Leadership team at the University of Missouri (MU) and the Replication Support Team at the University of New Mexico will train each ECHO Autism Hub in delivery and implementation of the intervention.

During the intervention phase, each ECHO Autism Hub team will provide twice-monthly 2-hour ECHO Autism Clinics for 15 PCP participants during a 6-month period. Each Clinic will utilize high quality, secure video conferencing technology to allow PCPs to interface with the ECHO Autism Hub team and all other participants, view documents, and view videos on screen (with minimal technological requirements for participants). The intervention will follow the protocol previously developed and tested by the ECHO Autism Leadership team. Based on this protocol, each ECHO Autism Clinic will include a didactic presentation, 2 to 3 PCP-generated case presentations, expert feedback and group discussion. Although the ECHO Clinic will include discussion of specific cases, no identifiable personal health information will be shared, individual patients will not be identified, and no direct patient care will be provided (PCP participants will maintain responsibility for care of their patients, but will develop new clinical skills through guided practice and collaborative learning). ECHO Autism didactic presentations will include use of AIR-P toolkits, guidelines, and algorithms to enhance medical care of children with ASD, with particular emphasis on identification/screening and management of co-morbid conditions. This combination of case-based learning, co-management with autism specialists, and didactic presentations provides multiple learning modalities for enhancing PCP knowledge and expertise.

Study Locations

The study will be implemented at 10 different ATN Sites (ECHO Autism Hubs): 15 PCP participants per ECHO Autism Hub will be recruited from the geographic region in which the ATN site is located.

1. Children's Hospital of Philadelphia
2. Lurie Center for Autism
3. University of Pittsburgh Medical Center
4. University of Rochester
5. Cincinnati Children's Hospital Medical Center
6. Nationwide Children's Hospital
7. Arkansas Children's Hospital/UAMS
8. Vanderbilt University Medical Center
9. The Center for Autism & Neurodevelopmental Disorders at UC Irvine

10. Toronto ATN Site (Holland Bloorview Kids Rehab)

Number of Planned Subjects

15 PCP participants from each ECHO Autism Hub will be enrolled (total enrollment = 150 participants)

Study Population

Participants will include primary care providers (PCPs) who provide care to children, whose patient populations are at least 50% underserved.

Assessment Groups

As noted above, a cluster-randomized design will be used, with sequential, staggered roll-out of the ECHO Autism intervention to 5 clusters over a 1 year period. The intervention will be delivered at 10 ECHO Autism Hubs, two being randomly assigned to each of the 5 clusters. Cluster assignment will determine the timing of the intervention start-date for each ECHO Autism Hub. Each ECHO Autism Hub will deliver the intervention to 15 PCP participants (for a total of 150 total participants). Participants will be assessed at four time points (as described below).

Duration of Assessment and Follow-up

Each PCP participant will complete a battery of assessments at four time points: Baseline/Pre-Intervention (T1), Mid-Intervention (T2), Post-Intervention (T3), and Follow-up (T4). The duration of the ECHO intervention will be 6 months, and the interval between each assessment point will be 3 months. The timeline of intervention and assessments by cohort is shown below:

	12/1/2016	3 Months	3/1/2017	3 months	6/1/2017	3 months	9/1/2017	3 months	12/1/2017	3 months	3/1/2018	3 months	6/1/2018	3 months	9/1/2018
Cohort 1	**T**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**								
Cohort 2			**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**						
Cohort 3					**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**				
Cohort 4							**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**		
Cohort 5									**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**

Measures

Primary outcome measures include: ASD knowledge, clinical practice/behavior and self-efficacy. ASD knowledge will be assessed at all timepoints using a 33-item test developed specifically for this study. Clinical practice/behavior will be assessed at all timepoints by chart review of a subset of charts from each PCP's practice. Self-efficacy in ASD screening and identification and treatment of medical co-morbidities will be assessed at all timepoints using a 57-item questionnaire that was developed for an ECHO Autism pilot study.

Secondary measures include: demographic and practice information, satisfaction, perceived barriers, participation, and a precise schedule of ECHO topics and dates of PCP chart reviews.

Glossary of Abbreviations

AAP	American Academy of Pediatrics
AIR-P	Autism Intervention Research Network on Physical Health
ASD	Autism Spectrum Disorder
ATN	Autism Treatment Network
DCC	Data Coordinating Center
ECHO	Extension for Community Healthcare Outcomes
HIPAA	Health Insurance Portability and Accountability Act
HRSA	Health Resources and Services Administration
IRB	Institutional Review Board
OHRP	Office for Human Research Protections
PI	Principal Investigator
SID	Study Identification Number
UNM	University of New Mexico

ETHICS/PROTECTION OF HUMAN SUBJECTS

Institutional Review Board (IRB)

This protocol and the recruitment letter (Appendix B) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The recruitment letter will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the letter will be given to the participant, and this fact will be documented in the participant's record.

Ethical Conduct of Study

This study will be conducted using good clinical practice (GCP), as delineated in *Guidance for Industry: E6 Good Clinical Practice Consolidated Guidance*, and according to the criteria specified in this study protocol. Before study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate IRB/REB. Any amendments to the protocol or to the consent materials must also be approved by the AIR-P CCC, AIR-P DCC, and appropriate IRB before they are implemented.

Compliance with 42 CFR Part 93, Public Health Service (PHS) Policies on Scientific Misconduct is implicit in the application for this proposal. The academic institutions participating in the ATN and this proposal have approved assurances and required renewals on file with the Office of Research Integrity (ORI) and compliance with these policies and procedures and the requirements of part 93 are in place. We understand and abide by the definitions of research misconduct per PHS policies (fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results).

Subject Information and Consent

Participants will include 150 primary care providers. Inclusion/exclusion, recruitment, consent, and enrollment are described in the sections below.

Subject Inclusion

Inclusion criteria for PCP participants are as follows:

- Current practice as a primary care provider (PCP).
- Currently providing care for children.
- Professional training in: general pediatrics, family medicine, advanced practice nursing (i.e. nurse practitioner or physician assistant).
- Active medical license in the state of practice.
- Patient population is at least 50% underserved.

Exclusion criteria are as follows:

- Not currently practicing as a primary care provider.
- Not currently providing care for children.
- Trainee status (e.g., medical student, intern, resident, or other pre-professional trainee).
- Subspecialist (e.g., psychiatrists, neurologists, developmental and behavioral pediatricians).
- Practicing within the same practice as another PCP Participant (i.e., only one PCP participant from any given practice may be enrolled as a research participant in the study).*

Study Modification/Discontinuation

*Providers who are not eligible to participate in the study, but who express interest in participating in ECHO Autism will be invited to join the Missouri ECHO Autism Clinic (an open-enrollment ECHO Clinic that does not currently include a research component).

The study may be modified or discontinued at any time by the IRB, HRSA, the AIR-P, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected.

BACKGROUND

Rationale

ASD is associated with significant impairments in social, communication and behavioral domains and medical and psychiatric comorbidities [1-3]. Unmanaged comorbid conditions contribute to increased stress and burden for families [4-5]. Children with ASD have increased risk for unmet healthcare needs, which is exacerbated among underserved populations [6-8]. Individuals in rural areas face socioeconomic and geographic barriers to accessing health care, including high rates of poverty [9]. They are more likely to lack health Insurance [10]. Rural areas have significant shortages of specialists, necessitating long distance travel for families to access services [10]. Rural children have higher rates of unmet medical and dental needs and of emergency department visits than do non-rural populations [11].

With increasing prevalence of ASD, diagnostic and treatment demands far exceed the capacity of specialty centers [12]. Early identification, referral and effective treatment are essential for enhancing outcomes, yet children with ASD face delays in diagnosis [13]. Although PCPs provide immediate and community-based care for children, they often feel ill-equipped to care for children with ASD [14-15]. Children with ASD experience co-occurring conditions that PCPs could manage, most notably sleep problems and constipation [3, 16-17]. However, PCPs report lack of knowledge and confidence in treating children with ASD, with resulting unmet healthcare needs [14-15]. PCPs also may lack the knowledge to manage ongoing psychotropic medication use. Lack of PCP comfort caring for children with ASD likely contributes to higher rates and duration of hospitalizations, greater expenditures, and greater use of psychotropic medications in children with ASD [18-21]. Thus, there is a critical need to improve early identification of ASD by PCPs and to enhance PCP effectiveness in managing sleep, constipation, psychotropic medications and other co-morbidities for children with ASD.

Extension for Community Healthcare Outcomes (ECHO) was designed to build local healthcare capacity and improve access to best practice care for minorities and underserved rural populations in New Mexico. ECHO represents an innovative telemedicine-based platform connecting local PCPs with specialists at academic medical centers during weekly ECHO clinics, and providing education in best-practice treatment protocols, case-based learning, and co-management [22]. The theoretical underpinnings of the model include well-established learning theories, all of which emphasize the need for collaborative learning, coaching, and mentorship from both experts and peers [23-26].

By equipping community-based providers to provide best-practice care, the ECHO model disseminates academic and specialty knowledge directly into families' communities. Mainly used to date for adult chronic conditions in rural communities, it has proven particularly effective with underserved and culturally-diverse populations. ECHO accelerates the adoption of effective interventions, guidelines, tools and systems management approaches to community practice, helping patients to receive care in their own communities. The ECHO model has demonstrated effectiveness in improving both provider self-efficacy and patient outcomes for Hepatitis C (HCV), and has now expanded to address other complex medical conditions, including rheumatoid arthritis, chronic pain, HIV/AIDS, addiction, and psychiatric problems, with rapid expansion into other geographic areas [22, 27-28].

Supporting Data

The results of an initial pilot study of the ECHO Autism intervention support its feasibility and effectiveness. The pilot project included development and implementation of the 6-month ECHO Autism curriculum, consisting of 2-hour clinics occurring twice per month, with a specific focus on 1) screening and identification of ASD symptoms and 2) management of medical and psychiatric comorbidities. Participants (n = 14 PCPs) completed measures of practice behavior and self-efficacy in screening and management of children with ASD at baseline (pre-test) and after 6 months of participation in ECHO Autism (post-test).The results revealed statistically significant pre- to post-test improvements in self-efficacy in all areas of ASD screening and management, in adherence to AAP autism screening guidelines, and in use of ASD-specific resources. Participants also reported high satisfaction with the program.

Risks and Benefits

Risks

There are minimal anticipated risks to PCPs for participation in the ECHO Autism intervention. The focus of the intervention is on improving knowledge and practice behavior through education and mentorship of PCP participants. No health-related or sensitive information about participants will be collected. Participant responses and data collected during study assessments will be de-identified.

Benefits

Participants will receive a 6-month intervention focused in improving their own knowledge, confidence and competence in managing children with ASD in their respective practices. Participants will receive direct benefits in the form of knowledge gained and continuing medical education credit. Participants may also expect to benefit from taking part of this research to the extent that they are contributing to the development and evaluation of new training methods, and that the information learned will benefit other PCPs and the children they serve in the future. Ultimately, the results of the study will benefit children with autism and their families by enhancing access to best-practice medical care in local communities.

OBJECTIVES

Study Objectives: To determine whether participation in a collaborative telehealth intervention will result in improved learning, clinical practice behavior and efficacy among primary care providers (PCPs).

Hypothesis 1: Following participation in ECHO Autism, PCPs will demonstrate significant improvements in ASD knowledge as assessed by pre- to post-intervention knowledge tests in ASD screening and identification and assessment and treatment of medical co-morbidities.

Hypothesis 2: Following participation in ECHO Autism, PCPs will demonstrate significant improvements in clinical practice/behavior as assessed by pre- to post-intervention chart reviews in ASD screening (co-primary outcome) and treatment of medical co-morbidities, in particular, sleep problems and constipation (co-primary outcome).

Hypothesis 3: Following participation in ECHO Autism, PCPs will demonstrate significant improvements in self-efficacy in ASD screening and identification and treatment of medical co-morbidities as assessed by pre- to post- intervention tests.

Study Outcome Measures

Primary outcome measures

1) **ASD Knowledge** will be assessed at T1, T2, T3, and T4 using a 33-item test developed specifically for the current study. The test is detailed in section 8.

2) **Clinical Practice/Behavior** will be assessed at T1, T2, T3, and T4 by review of a subset of charts from each PCP's practice. Five subsets of charts will be reviewed. The charts that will be reviewed are detailed in section 8.

3) **Self-Efficacy** will be assessed at T1, T2, T3, and T4 using a questionnaire developed for a previous ECHO Autism pilot study. The questionnaire is detailed in section 8.

Secondary measures

1) **Demographic and Practice Information** will be collected at T1 using a demographic questionnaire. Providers will report the following information: age, gender, race, ethnicity, zip code of practice, patient population (volume, patient characteristics), years of practice, provider type, and previous training in ASD.

2) **Satisfaction** will be assessed at T3 using a 12-item survey developed for a previous ECHO Autism pilot study. The survey includes 10 questions assessing overall satisfaction with participation in the ECHO Autism clinic (rated on a 5-point Likert-type scale), and two questions asking for overall comments and suggestions.

3) **Perceived Barriers** to caring for children with autism in primary care will be assessed at T1, T2, T3, and T4 by participant response to an 11-item checklist.

4) **Participation** in each ECHO session for a PCP will be abstracted from the CME sign in sheets.

5) **Precise schedule** of ECHO topics and dates of PCP chart reviews will be collected and considered as potential explanatory values for modeling outcomes, especially for the T2 assessment which occurs during the ECHO intervention.

STUDY DESIGN

Overall Study Design and Plan

A cluster-randomized design will be used, with sequential, staggered roll-out of the ECHO Autism intervention to 5 clusters of participants over a 1 year period. This design was chosen to maximize our ability to determine effectiveness of the intervention while minimizing potential contamination across groups and addressing potential ethical concerns. First, it would be problematic to randomize at the level of individual participants due to potential contamination across groups. Second, the staggered roll-out allows for comparison of each cluster to contemporaneous control groups as well as to its own baseline. Lastly, because of the anticipated benefit of the intervention for underserved populations, randomization of participants into a control group that does not receive the intervention would be unethical. The chosen design addresses these concerns by allowing us to randomize at the level of cohort (ECHO Autism Hubs), implement the intervention to cohorts in a stepwise manner, and test the effectiveness of the intervention using multiple data collection points under both baseline and ECHO conditions.

	12/1/2016	3 Months	3/1/2017	3 months	6/1/2017	3 months	9/1/2017	3 months	12/1/2017	3 months	3/1/2018	3 months	6/1/2018	3 months	9/1/2018
Cohort 1	**T**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**								
Cohort 2			**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**						
Cohort 3					**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**				
Cohort 4							**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**		
Cohort 5									**T1**	**ECHO**	**T2**	**ECHO**	**T3**		**T4**

Study Centers

The study will be implemented at 10 different ATN Sites (ECHO Autism Hubs): 15 PCP participants per ECHO Autism Hub will be recruited from the geographic region in which the ATN site is located.

1. Children's Hospital of Philadelphia

2. Lurie Center for Autism
3. University of Pittsburgh Medical Center
4. University of Rochester
5. Cincinnati Children's Hospital Medical Center
6. Nationwide Children's Hospital
7. Arkansas Children's Hospital/UAMS
8. Vanderbilt University Medical Center
9. The Center for Autism & Neurodevelopmental Disorders at UC Irvine
10. Toronto ATN Site (Holland Bloorview Kids Rehab)

Study Enrollment Procedures

Recruitment of Participants

Each ECHO Autism Hub will utilize a number of different recruitment strategies to recruit 15 PCP participants who meet inclusion criteria (as described previously). The Massachusetts League of Community Health Centers will work closely with each ECHO Autism Hub to facilitate recruitment efforts. Each ECHO Autism Hub team may generate a list of potential PCP practices based on publically available searchable databases. PCP practices may meet federal designation in any of the following:

- Primary Care Health Professional Shortage Areas (PC-HPSAs)
- Medically Underserved Areas and Populations (based on the Index of Medical Underservice)
- Federally Qualified Health Centers (FQHCs)

PCP practices are not required to meet these federal designations in order to be eligible for the study.

ECHO Autism Hub staff may then contact potential physicians via a recruitment letter or email that includes a link to ECHO Autism web-based resources. The letter can be followed by phone calls and/or face-to-face recruitment strategies as appropriate. Once a PCP agrees to participate, study staff will re-evaluate eligibility prior to consenting (based on inclusion/exclusion criteria described above).

Screening logs will be maintained to track recruitment efforts and results, including number of potentially eligible participants contacted, number of interested participants, and results of initial screening (reasons for ineligibility, reasons for nonparticipation of eligible participants).

Additional recruitment strategies may include:

- Attendance and/or presentations at local meetings such as the state chapters of the American Academy of Pediatrics (AAP), American Academy of Family Physicians, and State Primary Care Associations (FQHC).
- Social and traditional media posts
- Email recruitment through state-wide or regional primary care association listservs

Consent and Assent

A waiver of consent is being requested for the purpose of this study as this research involves no more than minimal risk. The waiver will not adversely affect the rights and welfare of the participants. Participants will be given a recruitment letter that outlines the research study for their review. A copy of this document is included as Appendix B. Participants will provide consent by their participation in the baseline/preintervention battery of assessments.

Study Duration

As noted above, a cluster-randomized design will be used, with sequential, staggered roll-out of the ECHO Autism intervention to 5 clusters over a 1 year period. The intervention will be delivered at 10 ECHO Autism Hubs, two being randomly assigned to each of the 5 clusters. Cluster assignment will determine the timing of the intervention start-date for each ECHO Autism Hub. Each ECHO Autism Hub will deliver the intervention to 15 PCP participants (for a total of 150 total participants). Participants will be assessed at four time points (as described below).

Duration of Assessment and Follow-up

Each PCP participant will complete a battery of assessments at four time points: Baseline/Pre-Intervention (T1), Mid-Intervention (T2), Post-Intervention (T3), and Follow-up (T4). The duration of the ECHO intervention will be 6 months, and the interval between each assessment point will be 3 months.

Participant Remuneration

Participants will receive $100 after completion of each time point.

Protocol Adherence

All ECHO Autism Hub teams will adhere to the procedures outlined in the Protocol, and will also adhere to the intervention implementation procedures described in the ECHO Autism Manual of Procedures throughout implementation of the 6-month ECHO Autism intervention.

STUDY ENROLLMENT AND WITHDRAWAL

Number of Study Subjects

Participants will include 150 primary care providers. Inclusion/exclusion, recruitment, consent, and enrollment are described in the sections below.

Inclusion and Exclusion Criteria

Subject Inclusion Criteria

- Current practice as a primary care provider (PCP).
- Currently providing care for children.
- Professional training in: general pediatrics, family medicine, advance practice nursing (i.e. nurse practitioner or physician assistant).
- Active medical license in the state of practice.
- Patient population is at least 50% underserved.

Subject exclusion criteria

- Trainee status (e.g., medical student, intern, resident, or other pre-professional trainee).
- Subspecialist (e.g., psychiatrists, neurologists, developmental and behavioral pediatricians).
- Practicing within the same practice as another PCP Participant (i.e., only one PCP participant from any given practice may be enrolled as a research participant in the study).

Treatment Assignment Procedures

Randomization procedures

The intervention will be delivered at 10 ECHO Autism Hubs, two being randomly assigned to each of the 5 clusters. Cluster assignment will determine the timing of the intervention start-date for each ECHO Autism Hub. Each ECHO Autism Hub will deliver the intervention to 15 PCP participants (for a total of 150 participants). Randomization of cluster assignment was completed by the DCC on 1/12/2016.

Reasons for withdrawal

Participation will be voluntary. Participants will not be withdrawn from the study unless they request to discontinue participation.

Handling of withdrawals

Data from withdrawn participants will be stored with data from participants who complete the study. No further data will be collected from participants who have withdrawn, and participant decisions to withdraw will be noted in the data collection system.

STUDY INTERVENTIONS

Interventions, Administration and Duration

During the intervention phase, each ECHO Autism Hub team will provide twice-monthly 2-hour ECHO Autism Clinics for 15 PCP participants during a 6-month period. Each ECHO Autism Hub will be comprised of a team of up to 5 autism specialists (Physician/Autism Specialist, Psychologist, Family Navigator, Dietician, and Parent Expert).

Each Clinic will utilize high quality, secure video conferencing technology to allow PCPs to interface with the ECHO Autism Hub team and all other participants, view documents, and view videos on screen (with minimal technological requirements for participants). The intervention will follow the protocol previously developed and tested by the ECHO Autism Leadership team. Based on this protocol, each ECHO Autism Clinic will include a didactic presentation, 2 to 3 PCP-generated case presentations, expert feedback, and group discussion. Although the ECHO Clinic will include discussion of specific cases, no identifiable personal health information will be shared, individual patients will not be identified, and no direct patient care will be provided (PCP participants will maintain responsibility for care of their patients, but will develop new clinical skills through guided practice and collaborative learning). ECHO Autism didactic presentations will include use of AIR-P toolkits, guidelines, and algorithms to enhance medical care of children with ASD, with particular emphasis on identification/screening and management of co-morbid conditions. This combination of case-based learning, co-management with autism specialists, and didactic presentations provides multiple learning modalities for enhancing PCP knowledge and expertise.

Each team will adhere to the intervention procedures described in the Manual of Procedures. The ECHO Autism Leadership team at the University of Missouri (MU) and the Replication Support Team at the University of New Mexico will train and mentor each ECHO Autism Hub in delivery and implementation of the intervention.

Adherence Assessment

Adherence/fidelity to the ECHO model will be assessed using a 25-item observer-rated form assessing fidelity of implementation including: training flow, facilitator engagement of participants, and other indicators of adherence. The measure was developed by the UNM ECHO Team to ensure that facilitators adhere to the model. Fidelity will be assessed by project leadership observing 3 randomly selected Clinics for each ECHO Autism Hub.

STUDY SCHEDULE

Screening

All providers who express interest in participation in ECHO Autism following initial recruitment efforts will be screened to ensure eligibility for the study. All providers who are screened will be tracked in a screening log maintained by each HUB. Screening will be conducted by phone, email, and a web-search of the state's medical accreditation agency to ensure that the provider meets the following criteria:

- Current practice as a primary care provider (PCP).
- Currently providing care for children.

- Professional training in: general pediatrics, family medicine, advanced practice nursing (i.e. nurse practitioner or physician assistant).
- Active medical license in state of practice.
- Patient population is at least 50% underserved.

Screen Failures

Providers who are not eligible to participate in the study, but who express interest in participating in ECHO Autism will be invited to join the Missouri ECHO Autism Clinic (an open-enrollment ECHO Clinic that does not currently include a research component).

Assessments

Each PCP participant will complete the battery of provider-completed measures (Section 7.2.1) at four time points: Baseline/Pre-Intervention (T1), Mid-Intervention (T2), Post-Intervention (T3), and Follow-up (T4). The duration of the ECHO intervention will be 6 months. The target time point for the T2 assessment is between the 6th and 7th ECHO sessions. The T3 assessment will occur within 4 weeks of completion of the final ECHO session. A final assessment will be conducted between 9 and 10 months after the start of the ECHO program.

In addition, chart reviews (Section 7.2.2) will be done in the same time frame for T1, T3, and T4. Because it would not be feasible to do the chart review in the two weeks for 15 participants, the T2 review will include charts from the 30 or 60 days before the 7th ECHO session for all participants.

Measures are listed below and described in section 8.

Provider-Completed Measures

1) **ASD Knowledge** assessed by a 33-item test of knowledge of ASD screening/identification, psychiatric co-morbidities, medical co-morbidities, and management of additional ASD-specific needs.

2) **Self-Efficacy** assessed by a 57-item questionnaire of self-efficacy in ASD screening, identification, and management of medical and psychiatric comorbidities.

3) **Demographic and Practice Information** assessed by self-report questionnaire at T1

4) **Satisfaction** will be assessed using a 12-item self-report survey at T3.

5) **Perceived Barriers** to caring for children with autism in primary care will be assessed at T1, T2, T3, and T4 by participant response to an 11-item checklist.

Chart Review Measures

1) **Clinical Practice/Behavior** will be assessed by review of a subset of charts from each PCP's practice. Study staff will complete chart reviews either in-person at each practice location or by remote review using an electronic medical record. Five subsets of charts will be reviewed with no more than 25 charts from each subset being reviewed. The charts that will be reviewed are detailed in section 8.

Process Measures

1) **Participation** in each ECHO session for a PCP will be abstracted from the CME sign in sheets.

2) **Precise schedule** of ECHO topics and dates of PCP chart reviews will be collected and considered as potential explanatory values for modeling outcomes, especially for the T2 assessment and chart review which occurs during the ECHO intervention.

Protocol Deviations

Any deviations from the protocol must be recorded in the research record and reported to the ECHO Autism Leadership team, the DCC, and the appropriate IRB.

CLINICAL ASSESSMENTS AND OUTCOME MEASURES

Primary Outcome Measures

1) **ASD Knowledge** will be assessed at T1, T2, T3, and T4 using a 33-item test developed specifically for the current study. The original test was developed and piloted with a group of 14 PCP participants, questions with very low difficulty were removed and/or reworded (e.g., if ≥ 90% of participants answered correctly at pre-test), additional questions were included to ensure that all content was adequately covered. The revised version was then piloted in a second sample of nine PCPs. The test assesses knowledge in the areas of ASD screening/identification, psychiatric co-morbidities, medical co-morbidities, and management of additional ASD-specific needs.

2) **Clinical Practice/Behavior** will be assessed at T1, T2, T3, and T4 by review of a subset of charts from each PCP's practice. Five subsets of charts will be reviewed, with a limit of 25 charts in any group. If more than 25 well-child visits at a specific age are available for chart review, the most recent 25 well-child visits at a specific age will be reviewed. The groups are:

   1.Charts for **all** children seen for **9-month well-child visits** in the **30 days prior** to the date of chart review (for assessment of ASD screening and referral practices).

   2. Charts for **all** children seen for **18-month well-child visits** in the **30 days prior** to the date of chart review (for assessment of ASD-screening and referral practices).

   3. Charts for **all** children seen for **24-month well-child visits** in the **30 days prior** to the date of chart review (for assessment of ASD-screening and referral practices).

   4. Charts for **all** children seen for **30-month well-child visits** in the **30 days prior** to the date of chart review (for assessment of ASD-screening and referral practices).

   5. Charts for **all children with ASD** in the **60 days prior** to the date of chart review (for assessment comorbidity management).

3) **Self-Efficacy** will be assessed at T1, T2, T3, and T4 using a questionnaire developed for a previous ECHO Autism pilot study. The questionnaire is comprised of 57 items across five domains: 1) ASD screening and identification (7 items), 2) ASD referral and resources (9 items), 3) assessment and treatment of medical comorbidities (19 items), 4) assessment and treatment of psychiatric comorbidities (13 items), and 5) Additional (9 items). Participants report the degree to which they are confident in their ability to provide effective care in each domain. Items are rated on a 6-point Likert-type scale (ranging from 1= "no confidence" to 6 = "highly confident/expert").

Secondary Measures

1) **Demographic and Practice Information** will be collected at T1 using a demographic questionnaire. Providers will report the following information: age, gender, race, ethnicity, zip code of practice, patient population (volume, patient characteristics), years of practice, provider type, and previous training in ASD.

2) **Satisfaction** will be assessed at T3 using a 12-item survey developed for a previous ECHO Autism pilot study. The survey includes 10 questions assessing overall satisfaction with participation in the ECHO Autism clinic (rated on a 5-point Likert-type scale), and two questions asking for overall comments and suggestions.

3) **Perceived Barriers** to caring for children with autism in primary care will be assessed at T1, T2, T3, and T4 by participant response to an 11-item checklist

4) **Participation** in each ECHO session for a PCP will be abstracted from the CME sign in sheets.

5) **Precise schedule** of ECHO topics and dates of PCP chart reviews will be collected and considered as potential explanatory values for modeling outcomes, especially for the T2 assessment which occurs during the ECHO intervention.

Intervention Fidelity Evaluations

1) **ECHO Fidelity** will be assessed using a 25-item observer-rated form assessing fidelity of implementation including: training flow, facilitator engagement of participants, and other indicators of adherence. The measure was developed by the UNM ECHO Team to ensure that facilitators adhere to the model. Fidelity will be assessed at 3 randomly selected Clinics for each ECHO Autism Hub.

STATISTICAL ANALYSIS PLAN

Statistical Considerations

Data Analysis

There are two co-primary endpoints (the percent of children being screened for autism, with the chart reviews for children of all ages combined; and the percent of co-morbidity management of autistic children in the practice). To preserve the overall study Type I error at 0.05, we will use an alpha-level of 0.025 for each of the two endpoints separately.

Standard summary statistics (e.g. median/IQR) will be calculated separately for each center (ECHO HUB) and PCP within center separately for each time point. The results will be presented separately for each center over time using a spaghetti plot. Graphs will also be prepared to present the results of each PCP within a center.

The primary outcome analysis will use a generalized mixed model analysis, using a binary distribution and logit link for each outcome (patient screened / not screened or patient received / did not receive appropriate co-morbidity management). Treatment effect and trend over calendar time will be fixed effects in the model. The model will include center, PCP within center, and nominal study period of the observation as random effects. The primary analysis will use data from T1 (baseline) and T3 (post-intervention). The determination of the utility of the ECHO intervention will be based on these results.

An additional analysis of both primary endpoints will use data from T1, T2, and T3. The model described above will be expanded to incorporate the precise timing of the T2 assessment for the PCP and allow for the estimated impact of the ECHO training through that time point on each of the measures separately. For example, the change in co-morbidity management at the T2 assessment would likely depend on the number of sessions devoted to the topic prior to the T2 assessment for the specific PCP.

For the screening endpoint, a secondary analysis will include a factor for age group and age group x treatment interaction to determine whether screening changes were related to the age group.

One complication with our approach is that if a PCP practice has no autism patients at the start of the study, then the change in practice for autism patients over time will be uninformative. We anticipate that this will occur in very few practices, but we will perform an additional analysis of the number of autism patients in each practice using a similar approach but using a Poisson distribution and log link in the analysis.

A similar analysis approach to the primary analysis will be used for the other endpoints collected over time (e.g. ASD knowledge and self-efficacy measures), with appropriate adjustment of the model for the distribution of the outcome variable. The primary analysis for these endpoints will use results from T1, T2, and T3 only, and use the time on intervention as the estimate of the predicted treatment effect for period T2.

An additional analysis of the primary endpoints, ASD knowledge, and self-efficacy will use data from T3 and T4 only. The purpose of this analysis is to determine if there is a practice / skills / self-efficacy decline after the ECHO program ends.

For data available at only a single time-point (e.g. satisfaction), results will be summarized separately for each center and compared across centers using a Kruskal-Wallis test.

Exploratory analyses will consider the effect of PCP demographic and practice information on the treatment effect on the primary endpoints.

Power Considerations

Given the complexity of the proposed analysis, power calculations were based on simulations. The data generation process allowed for random effects for center, PCP within center, and nominal period. There was no time trend in the data, although a potential time trend as a fixed effect was included in the model. Simulations were done for 10 randomly selected seeds (from several different websites and different random number tables), 1000 simulations per seed. The data generating process allowed for approximately a 50% intra-class correlation for the PCP within group effect, reflecting the possibility that the impact of ECHO would be correlated within each center, even with good fidelity to the intervention program. Simulations allowed for varying numbers of patients per PCP practice.

If there are on average 5 patients per PCP (e.g. 5 autistic patients seen in the last 60 days), we would have over 90% power to detect an increase of 15% in appropriate co-morbidity management (alpha=0.025, two-sided). If there are 15 patients per PCP on average (e.g. 15 patients with well child visits in the past month), we would have over 90% power to detect an increase of 10% in autism screening (alpha=0.025, two-sided). If the number of patients per PCP was higher, then we would have over 90% power for even smaller differences. Results were consistent for the different seeds.

DATA COLLECTION, MANAGEMENT, AND MONITORING

Role of Data Management

Web-Based Data Collection and Management System

Data collection will occur via a web-based data entry system to allow easy access to enrollment 24 hours a day, seven days a week. Participants will complete assessments using an online portal.

Certification in the Use of Web-Based Data Entry System

The DCC will provide training and certification of study staff in the use of the data entry system. Once certified, users are permitted to enter data into the production system. Access is password controlled. Certification for use of the web-based data entry system will be completed via individual practicum assessment.

Participants will be trained by study coordinators in the use of the EDC portal.

Data Entry and Checks

Data for individual participants will be recorded on electronic case report forms (eCRF) in an electronic data capture system. All participants screened for the study, including the screen failures, must be entered into the system. The EDC will reflect participant status (screen failure, enrolled, early termination, completed) at each

phase during the course of the study. Participants will not be identified on the eCRFs by name or initials. Each participant will be assigned a study identification number.

Clinical data processing and management will be employed based on the procedures developed in conjunction with the AIR-P DCC. All of the data entered into the electronic data capture system will be checked for valid values and ranges, between-item logical consistency, and within-subject variation.

Quality Assurance

Prior to the initiation of the study, an investigator's meeting will be held with the AIR-P CCC, AIR-P DCC, the investigators and their study coordinators. This meeting will include a detailed discussion of the protocol, performance of study procedures, safety reporting requirements, electronic data capture system training and eCRF completion and simulation of study procedures, as applicable. Study staff that is responsible for the collection and submission of the study data will be required to pass eCRF training for certification prior to use of the production system for submission of the data. The study Manual of Procedures will be reviewed during training for site personnel and should be utilized to reference key details regarding study processes.

After completion of the entry process, computer logic checks or Integrity reports will be executed to assess data inconsistencies (e.g., inconsistent study dates). A response to these reports is required from site personnel by the defined report date. In addition, data modifications to the data field(s) must be made in the electronic data capture system which tracks the audit history of all data entered and modified.

Data Handling and Record Keeping

Confidentiality

Raw data will be stored in locked cabinets in a locked office at each site. All evaluation forms, reports and other records that leave a site will be identified only by the Study Identification Number (SID) to maintain participant confidentiality. De-identified data will be submitted to a central, password-protected database provided by the DCC. The key connecting participants to their SID will be secured in a locked cabinet at each site. All computer entry and networking programs will be done using SIDs only. Data forms will only be identified by SID. A limited personal identifier (email address) will be collected in the EDC in order for the EDC to send out automated reminders for participants to complete the online portal assessments. For participants not wishing to provide this, the site will be responsible for contacting participants about completing the online portal assessments. The database will not contain any other personal identifiers other than study identification number.

ECHO clinics utilize secure video conferencing technology that meets VTC industry standards H.264, H.265, H.239, H.323 and SIP. Although the ECHO Clinic will include discussion of specific cases, no identifiable personal health information will be shared.
Chart reviews will be conducted on-site by study staff. For research purposes, the results from the record reviews (for chart reviews groups 1 to 4: the number of individuals screened / well-child visits by age group; for chart reviews group 5: the number of individuals receiving co-morbidity management / number of ASD visits in past 60 days will be summarized from these source data. PHI will be removed and records will be identified with a unique identifier generated by Project ECHO. Study staff will be trained on the importance of confidentiality and HIPAA requirements.

Retention of records

Sites will comply with their individual IRB's policies for retention of records.

Publications

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by AIR-P and HRSA prior to submission.

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