Project EARLY
Early Identification And Service Linkage For Urban Children With Autism: A Randomized Controlled Trial

ClinicalTrials.gov number: NCT02359084
Funding Mechanism: National Institute of Health/ National Institute of Mental Health
Award#: 1R01MH104355
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1 List of Abbreviations

Abbreviation	Abbreviation definition
ASD	Autism Spectrum Disorder
BMC	Boston Medical Center
BUMC	Boston University Medical Campus
CCM	Conventional Care Management
CHOP	Children's Hospital of Philadelphia
CT	Connecticut
DBP	Developmental and Behavioral Pediatrics
DSMB	Data Safety Monitoring Board
FN	Family Navigation
IRB	Institutional Review Board
ITT	Intent-to-treat
MA	Massachusetts
MCHAT-R/F	Modified Checklist for Autism in Toddlers-revised with follow up
PA	Pennsylvania
PI	Principal Investigator
PCP	Primary care provider
PN	Patient Navigation
RA	Research Assistant
RCT	Randomized Controlled Trial

2 Protocol Summary

Title:	Early Identification And Service Linkage For Urban Children With Autism
Population:	250 children ages 15-27 months identified with a positive MCHAT-R/F screen in primary care (or for whom there are clinical concerns for autism) who are referred for an autism evaluation
Intervention:	Families will be randomized to FN or CCM. FN families will be assigned a navigator who conducts community-based outreach to families to address structural barriers to care and support engagement in recommended services. The goal of FN during the diagnostic evaluation period is to ensure timely completion of the evaluation. The focus of these interactions is to understand the structure and purpose of the evaluation, gather and complete required materials, and address logistic barriers related to the diagnostic visit. CCM families will be assigned to a care manager. Consistent with a high-quality medical home, the care manager is responsible to ensure that the referral for the diagnostic evaluation has been made. She will also be available for family-initiated support. The care manager will be responsible

	for ensuring that referrals are made and continue to provide family-initiated, clinic-based support to families. Families will receive FN or CCM following a positive initial screen and for 100 days after diagnostic ascertainment.
Objectives:	Goal 1. To assess the effect of Family Navigation (FN) as compared to conventional care management (CCM) to shorten the time to diagnosis among children suspected to have ASD; shorten the time to deployment of ASD services among those diagnosed; and improve engagement with ASD services Goal 2. To document the proportion of the study sample that is diagnosed with ASD or another developmental condition Goal 3. To assess the role of caregiver stress, burden, and behavioral activation as potential intervention mediators; and practice site and race/ethnicity as potential intervention moderators.
Design/Methodology:	Our overall design is a Type 1 Effectiveness-Implementation Hybrid design, whereby we test a systemic FN protocol within a randomized design, while concurrently gathering information on FN's delivery to inform its potential for ultimate dissemination and implementation. **This protocol covers the randomized controlled trial.** Randomization will happen after referral to an autism evaluation. FNs will meet in-person with families at three timepoints: before the evaluation to provide psychoeducation, after the evaluation to discuss diagnosis and recommended services, and 100 days after receipt of diagnosis to review families' progress and next steps. Care managers will contact the families by phone after referral for an evaluation. They will be available to answer questions related to the evaluation, appointments, etc. All subsequent contacts with the care managers beyond the introductory call must be initiated by the parent. Care managers will not be available to meet in-person with patients
Total Study Duration:	February 12, 2015- July 27, 2020
Subject Participation Duration:	12 months

3 Background/Rationale & Purpose

3.1 **Background Information**

3.1.1 Description of the health issue and research question.

Tools to identify and diagnose very young children with ASD have been validated[1–6], and recommendations for universal ASD screening at the 18 or 24-month health supervision visit have been adopted by all major pediatric professional societies[7,8]. Although evidence that interventions for very young children can impact the core deficits of ASD continues to grow,[9–12] systems changes that support universal screening, comprehensive evaluation, and timely access to services have not kept pace with advances in diagnosis and treatment.[13–15] Furthermore, despite a secular trend toward earlier identification of ASD,[16–20] minority and low-income children continue to be diagnosed later than white and more financially advantaged children.[16,21–25] Once diagnosed, minority children receive fewer and lower quality services[24] and they wait longer to receive these services.[23,26–28] Feasible, systemic interventions with broad scale-up potential are necessary to decrease racial and ethnic disparities in identifying children with ASD and in providing them timely, high quality services.

Our dual goal to reduce existing disparities and improve early ASD identification and linkage to services underlies the rationale for the setting of this study– three urban primary care networks (in Philadelphia- CHOP; in New Haven-Yale University; in Boston- Boston Medical Center) affiliated with academic Developmental and Behavioral Pediatrics (DBP) autism specialty clinics. These systems represent the types of integrated, real world settings that care for poor and minority families in cities across the US and support the potential for broad intervention dissemination and implementation.

3.2 **Research Question.**

Does Family Navigation (FN), an individually-tailored, culturally-informed care management strategy, increase the likelihood of achieving diagnostic ascertainment among low-income, racial/ethnic minority children who screen positive for autism spectrum disorder (ASD)?

3.3 **Brief description of the study intervention**

We propose a parallel group, randomized trial of 15-27-month-old children attending health supervision visits at one of our three study sites. One group will receive a systemic FN protocol, which includes support for diagnostic evaluation; referral to treatment; and engagement in treatment. Control group subjects will receive conventional care management (CCM), which is designed to be consistent with the type of care provided within a traditional – but high quality – patient centered medical home.

Patient navigation (PN) is a theory-based and empirically-supported care management strategy.[29,30] It differs from other care management strategies in that it focuses on overcoming patient-specific barriers to a defined set of services over a defined, time-limited period. PN is well established in cancer care as a means to reduce disparities in outcomes.[30, 31,32] Emerging evidence of its efficacy among cancer patients demonstrates that it shortens the critical interval between a positive screening test (for example, a mammogram for breast cancer) and definitive diagnosis,[33–35] decreases anxiety,[36] and increases satisfaction with services.[36] The goal of navigation is to integrate a disjointed health care system on behalf of an individual patient. In this study, we will build upon the established principles of Navigation but expand the navigator role in novel ways. Navigation services will be provided to the family unit by bilingual paraprofessionals and referred to as Family Navigation (FN). It will be extended to integrate a fragmented network of ASD services that requires coordination among community-based and educational services, as well as those provided by the conventional health care team.

Additionally, FN will be augmented with theory-based behavior change strategies – motivational interviewing and collaborative decision making – that support patient engagement and self-management skills. A typical FN activity may be to assist a parent with marginal literacy to complete a clinic's patient questionnaires, help a family know what to expect during a stressful ASD diagnostic evaluation, or coordinate childcare around a child's early intervention schedule. In this study, the systemic FN protocol will begin at the time of a child's referral for an autism evaluation, and end 100 days after diagnostic resolution – at which time, a child with ASD would be expected to be engaged in intensive early intervention services (based on the guidance from Autism Speaks). [37]

CCM will be delivered by care managers who will contact the families by phone after referral for an evaluation. They will be available to answer questions related to the evaluation, appointments, etc. All subsequent contacts with the care managers beyond the introductory call must be initiated by the parent. Care managers will not be available to meet in-person with patients

3.4 **Pertinent prior experience with the intervention.**

To date, we have conducted two small-scale randomized trials of FN – each focusing on its feasibility during discrete periods of time within the broader trajectory between initial ASD screening and ultimate service provision:

> **Diagnostic Period**. Our first trial (Feinberg R03HS22155) concerns the period between an initial suspicious ASD screen and diagnostic resolution. Data from this ongoing pilot RCT (N=27) demonstrate the feasibility of trialing FN more broadly across the 3 sites proposed in the current application. Specifically, training navigators to fidelity in the FN model requires only a 4-day training; supervising navigators requires only a weekly one-hour supervision session; and investigators know of no adverse events that could jeopardize the safety or welfare of either the lay navigators or the families they serve. Furthermore, although we interpret group-to-group comparisons in pilot studies with extreme caution,[38,39] our pilot data provide suggestive evidence of FN's potential to improve timely diagnosis. Thus far, 90% of children who received FN in this pilot study completed a diagnostic evaluation for ASD, compared to 24% who received usual care.
>
> **Engagement with Treatment**. Our second trial (Augustyn R40MC19928) concerns the period beginning with definitive ASD diagnosis and ending 6 months later, when the child should be fully engaged with services. This trial provided rich process data that constituted the basis of important intervention refinements for the present trial. In this trial, 76 of 78 parents randomly allocated to the FN arm actively engaged with their navigators to access treatment and entitlement services. Navigators spent an average of 15 hours with each family over the course of the 6-month intervention. During this time, families received an average of 6 in-person visits, 17 phone contacts and 4 email contacts. Accessing services accounted for 58% of documented navigator person-time, followed by accessing public benefit programs. We assessed for potential contamination in this trial and found that all participants received the intervention as assigned.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.5 **Rationale and Purpose**

This study is a replicable, comprehensive service intervention within the type of health system where most urban children receive routine health care. This multisite collaboration is an example of the type of practice-based research network that can serve as a laboratory for testing replicable systems innovations with strong potential for widespread adoption and use.[40] Given the near universal participation of US children in primary care, a primary care-based intervention has broader reach than other possible settings and maximizes the number of children who might benefit from proposed systems changes.[41]

4 Objectives

4.1 **Study Objectives**

Goal 1. To assess the effect of Family Navigation (FN) as compared to conventional care management (CCM) to shorten the time to diagnosis among children suspected to have ASD; shorten the time to deployment of ASD services among those diagnosed; and improve engagement with ASD services

Goal 2. To document the proportion of the study sample that is diagnosed with ASD or another developmental condition

Goal 3. To assess the role of caregiver stress, burden, and behavioral activation as potential intervention mediators; and practice site and race/ethnicity as potential intervention moderators.

4.2 **Study Outcome Measures**

For all children enrolled in the trial (n=250), data on screening and diagnostic outcomes (from the child's problem list) will be abstracted electronically from the child's medical record. We will more obtain more detailed demographic and outcome data for children who fail the initial M-CHAT-R/F screen and whose families provide written, informed consent. Confirmatory screening results, referrals to care, and service use will be obtained from care manager and navigator logs and from the child's medical, early intervention, and ASD service provider records. We will also collect data on satisfaction with services and, among the FN group, relationship with the assigned navigator during final research assessment. There are 3 follow up data collection points: after diagnostic evaluation, 100 days after receipt of diagnosis, and 1 year after study enrollment.

4.2.1 Primary Outcome Measures

1. Diagnostic interval: Number of days defined as beginning the day of the positive confirmatory screen and ending the day when the family receives a determination (yes/no) of ASD diagnosis
2. Time to receipt of ASD services/recommended services: Number of days from date of diagnosis to receipt of recommended services

4.2.2 Secondary Outcome Measures

1. Determination of ASD diagnosis (based on DSM V criteria made by a Board Certified DBP Pediatrician. Assessments are based on site protocols; all use standardized, validated measures appropriate for very young children.)[42–45] [Time Frame: 1 year]. Determination of ASD diagnosis will be based on DSM V criteria made by a Board Certified DBP Pediatrician. Assessments are based on site protocols; all use standardized, validated measures appropriate for very young children.
2. Satisfaction with Family Navigator (Patient Satisfaction with Interpersonal Relationship with Navigator (PSN-I)) [Time Frame: 100 days after developmental assessment completion]. The Patient Satisfaction with Interpersonal Relationship with Navigator (PSN-I) is a newly validated 9 item scale to assess satisfaction with the interpersonal relationship with the navigator.[46–48]

4.2.3 Other Outcome Measures:

1. Perceived Stress Scale - Self Report (PSS) [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. The Perceived Stress Scale is a measure of the degree to which situations in one's life are appraised as stressful. The questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way.; lower scores are more favorable.[49]
2. Parenting Stress Index - Short Form[50–52] (PSI-SF) [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. This measure is a brief version of the Parenting Stress Index, a widely used and well-researched measure of parenting stress. The PSI-SF has 36 items from the original 120-item PSI. Items are identical to those in the original version. It was developed in response to clinicians' and researchers' need for a shorter measure of parenting stress and was based on factor analysis of the original PSI, which suggested the presence of three factors. It yields scores on the following subscales: 1) Parental Distress, 2) Parent-Child Dysfunctional Interaction, and 3) Difficult Child. Similar to the full PSI, it also has a validity scale.
3. Brief COPE[53] [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. The Brief COPE is designed to measure parents' coping strategies, including problem-focused coping, avoidant coping, and social coping
4. Pearlin Mastery Scale [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. The Pearlin Mastery Scale[54] is designed to measure self-concept and references the extent to which individuals perceive themselves in control of forces that significantly impact their lives. Total score can range from 7 to 28 points; higher scores are more favorable
5. VR12 Health Survey [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. The VR-12 includes 12 original question items from the VR-36. The questions in this survey correspond to seven different health domains: general health perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy/fatigue levels, social functioning and mental health.[55]

6. Medical Outcomes Study-Social Support Survey (MOS-SSS) [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. This is a brief, multidimensional, self-administered, social support survey that was developed for patients in the Medical Outcomes Study (MOS), a two-year study of patients with chronic conditions. This survey was designed to be comprehensive in terms of recent thinking about the various dimensions of social support.[56]
7. Family Impact Questionnaire[57] (FIQ) [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. The FIQ measures parent's perceptions of their child's impact on family functioning.
8. Autism Parenting Stress Index (APSI) [Time Frame: 1-4 weeks after developmental assessment completion, 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. Screening and triage measure for evaluating the parenting system and identifying issues that may lead to problems in the child's or parent's behavior. Focuses on three major domains of stress: child characteristics, parent characteristics and situational/demographic life stress.[58]
9. Adaptive Behavior Assessment System[59] (ABAS) [Time Frame: 1 year after failed confirmatory screen]. The ABAS measures functional and adaptive skills overall and on sub-scales including communication, self-direction, and social skills.
10. Brief Illness Perception Questionnaire[60] [Time Frame: 1 year after failed confirmatory screen]. This 9 item scale assesses emotional and cognitive perceptions of illness.
11. Hospital Care Questionnaire[61] [Time Frame: 100 days after developmental assessment completion, 1 year after failed confirmatory screen]. This questionnaire assesses satisfaction with hospital/medical staff and processes during care experiences.
12. Engagement in treatment [Time Frame: 1 year]. Number of hours of ASD/general developmental services will be assessed using Part C early intervention service data.
13. Mullen Scales of Early Learning (MSEL)[62] [Time Frame: 1 year after failed confirmatory screen]. This tool assesses developmental status in the areas of Visual Reception, Fine Motor, Receptive Language, and Expressive Language scales.
14. Vineland Adaptive Behavior Scales-3[63] [Time Frame: 1 year after failed confirmatory screen]. Parent/caregiver report child functioning in the areas of social interactions, communication, and daily living skills.
15. Autism Diagnostic Observation Schedule-2[44] (ADOS-2) [Time Frame: at time of evaluation and 1 year after failed confirmatory screen]. The ADOS assesses communication and repeated and restricted behavior to diagnose children with autism spectrum disorder.

5 Study Design

5.1 **Type/Design of Trial.**

We propose a parallel group, randomized trial of an estimated 250 families of 15-27-month-old children attending health supervision visits at one of our primary care study sites. One group will receive a systemic FN protocol, which comprises five integrated components specifically targeting universal screening; implementation of a decision rule for referral for ASD evaluation; expedited diagnostic evaluation; referral to treatment; and support for engagement in treatment.

Control group subjects will receive conventional care management (CCM), which is designed to be consistent with the type of care provided within a traditional – but high quality – patient centered medical home.[64]

5.2 **Randomization process.**

After completing the baseline assessment, participants (parent-child dyads) will be randomized 1:1 to FN or Conventional Care Management (CCM) using randomly permuted blocks of 2 and 4. Participants were stratified by primary care site and receipt of pre-screening educational materials. Randomization lists were generated for each site by a secure web-based data management system, StudyTRAX. Investigators and staff responsible for data collection were masked to study allocation.

Data collection for assessment of primary outcomes. Data will be collected from participant electronic health records, in-person face-to-face interviews and assessments, and records of developmental services.

6 Potential Risks and Benefits

6.1 **Risks**

1. The primary potential risk to subject is psychological because the research covers the subject of autism, a disabling and chronic condition that has long term impact on a child's development, it may be emotionally distressing to individuals in the study.
2. Although we will strive to maximize the cultural sensitivity in delivery of the proposed intervention, it is possible that certain individuals' explanatory models of their child's condition will be incompatible with our proposed intervention. This has the potential to upset study participants.
3. Although we will make every effort to store data in a secure and confidential manner, breaches of confidentiality may occur accidentally.
4. On rare occasions, information may be obtained that may require mandatory reporting, (for example, if we observe physical abuse during a research assessment). Although we have developed protocols to address such scenarios (sites will follow their mandatory reporting procedures), they will invariably be upsetting.
5. Possible but unlikely occurrences include psychological distress. It is unlikely that a family navigator will precipitate psychological distress as this type of activity is preventative and supportive in nature and does not explicitly address mental health conditions or stress. Family Navigation allows for clients to discuss their family practical life problems (transportation, insurance options, making appointments and handling paperwork) and leaves it up to the client to pick the barriers they want to address, with their family navigator. However, in the event that a significant psychological distress occurs, the Principal Investigator will be available via pager; and weekly supervision meetings will also be held to support staff through any events.

6.1.1 Protections against risks

Dr. Feinberg has extensive experience training bilingual, bicultural research assistants to work with community-based projects. The research team will reflect the racial, ethnic, and cultural diversity of families seen at the BMC DBP clinics which will help secure culturally appropriate care.

Many measures will be taken to ensure confidentiality (see section 11.1). Since we have measures in place to protect confidentiality, if such breach is determined to have happened, we will consider this event to be an Unanticipated Problem. We will:

1. Contact all subjects whom the breach affected immediately, explain to them exactly what happened, and to our best approximation who had access to the data
2. Contact the BUMC IRB as soon as possible and within two business days of learning of the event
3. Review events and develop a corrective plan to minimize the likelihood that such event reoccurs

We perceive that the most serious potential risk to study participants is to observe physical abuse during a research assessment or meeting with a FN and not have an adequate way to deal with this. We will implement the following procedures to train staff how to address these risks:

1. FN and research staff will be trained in mandated reporting requirements and protocols to follow in the event that sometime is witnessed in the home or during an interaction with the family that is concerning
2. FN and research staff will be trained in responding to psychological distress
3. Throughout the study, FNs will meet regularly and review cases to discuss concerns
4. Research staff who conducts outcome assessments (they will not be navigators or care managers in order to maintain blinding) will meet with the project manager regularly to discuss concerns
5. FN and research staff will have the site PIs pager and, per protocol, will page her to discuss any concerning events at the time of the witnessed event

6.2 **Potential Benefits**

The potential long-term benefits of this study plan outweigh its risks. All children who demonstrate risk for ASD based on their failed MCHAT-R/F[65] screen will receive services that exceed those currently provided. The systematic completion of the M-CHAT-R/F and guarantee of an expedited ASD evaluation for those who fail the M-CHAT-R/F, which is available to all participants, regardless of treatment arm, is an enhancement to usual care at participating sites. Individuals not directly involved in this work stand the opportunity to benefit from the knowledge we gain from the study.

From a practice-based perspective, the project deliverables will assist interested practices and health insurers to implement the family navigator model outside of a rigorous research environment. At present, low income and minority children are not diagnosed with ASD as early as their white and more advantaged peers and, thus, do not receive recommended services during the period when they are most likely to improve outcomes. We hope that the proposed services system intervention will demonstrate efficacy as a feasible and acceptable strategy to promote timely identification of ASD, improve linkage and engagement to ASD treatment and services. Our plan to test Family Navigation in the types of primary care settings in which low-income, ethnically diverse children receive routine health care services will provide valuable information to primary care practices and integrated health networks about the potential benefits and barriers to implementing this type of intervention for children with ASD.

6.3 **Analysis of Risks in Relation to Benefits**

We believe that our study represents an innovative approach to addressing disparities in time to diagnosis among young children with ASD and far outweighs the risks. In fact, it establishes a structure to support families to be prepared and activated advocates for their children. The parent intervention, patient navigation, which we have broadened to encompass the family, has demonstrated effectiveness in a variety of settings in decreasing delays in diagnosis and improving a patient's experience. The study will allow us to test family navigation among children at risk for delays in ASD diagnosis. The intervention model, which could easily be expanded to children with a range of developmental concerns, has the potential for replication and widespread dissemination.

7 Study Subject Selection

7.1 **Subject Inclusion Criteria**

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Child age 15 to 27 months who receive care at one of the study's primary care recruitment sites.
- Autism risk based on standard scoring protocol of M-CHAT R/F
- PCP clinical concern

7.2 **Subject Exclusion Criteria**

An individual who meets any of the following criteria will be excluded from participation in this study:

- Children with a prior diagnosis of ASD
- Families with immediate plans to leave the area if they plan not to follow through with the developmental assessment at Boston Medical Center, CHOP, or Yale due to geographic location.
- Children in foster care

8 Study Intervention

8.1 **Overview.**

The FN and CCM protocols will begin after a child is identified as at risk for ASD and referred for a diagnostic evaluation. FN and CCM families will have the support of their navigator/care manager for up to 100 days after completion of the diagnostic assessment – at which time, a child with ASD would be expected to be engaged in intensive early intervention services (based on the guidance from Autism Speaks). Both FN and CCM arms will have full access usual services at their primary care sites, the specialty referral clinic, and each state's ASD services network.

8.2 **Intervention.**

FN is based on patient navigation, which is a theory-based, empirically-supported, multicomponent, care management strategy.[29,30] It differs from other care management strategies in that it focuses on overcoming patient-specific barriers to a defined set of services over a defined, time-limited period. PN is well established in cancer care as a means to reduce disparities in the critical interval between a positive screening test (for example, a mammogram for breast cancer) and definitive diagnosis,[33–35] decrease anxiety,[36] and increase satisfaction with services.[36] The goal of PN is to integrate a disjointed health care system on behalf of an individual patient. FN builds upon the established principles of PN but expands the navigator role in novel ways and renames the intervention. Navigation services are provided to the family unit by bilingual paraprofessionals. It is extended to integrate a fragmented network of ASD services that requires coordination among community-based and educational services, as well as those provided by the conventional health care team. Additionally, FN is augmented with evidence-based behavior change strategies – motivational interviewing and collaborative decision making – that support patient engagement and self-management skills.

Families randomized to receive FN will meet with their navigator for 3 in-person visits: before the child's ASD evaluation to receive materials to promote family engagement and strengthen family understanding of developmental norms; after the child has been diagnosed to review recommended services and support families to access services; and 100 days after receipt of diagnosis to review the family's progress and connection to services. Additional contacts with the navigator will be based on family preference and need. Contacts between families and the navigator may be in-person at any place of the family's choosing, in addition to use of text, phone call, email, fax etc. A typical FN activity may be to assist a parent with marginal literacy to complete a clinic's patient questionnaires, help a family know what to expect during a stressful ASD diagnostic evaluation, or coordinate childcare around a child's early intervention schedule. Navigators will follow a standardized protocol, keep extensive structured logs of their work, and have a random subset of encounters between them and families audio recorded. Data will be captured on all interactions with families, providers, medical, educational, and social service organizations, recording time spent, activities performed, and barriers addressed.

8.3 **Control Intervention.**

CCM exceeds usual care at all sites and will be provided in addition to existing procedures. CCM will be guided by manualized protocol that includes outreach to families and the child's primary care provider (PCP) and a designated direct line to reach the care manager. Outreach to families will consist of an introductory call, during which care managers will remind families about their child's developmental assessment intake appointment, offered to answer questions about the assessment and developmental services, and provided resources to community services to address social needs. Outreach to the child's PCP will include a letter to introduce the role of the care manager and provide contact information. CCM will be delivered by designated care managers, who will be existing staff at the study sites. They will have access to all resources at their site, including interpreter services. All contacts with care managers in the CCM arm, beyond the introductory phone call, must be parent-initiated.

9 Study Procedures

9.1 **Recruitment**

All children are screened using the MCHAT-R/F[65] at their 18 month or 2-year well-child visit as part of routine care. Children at participating sites who fail the MCHAT and/or whose provider

has high suspicion of ASD will be referred to the study coordinator, who will complete the MCHAT-R/F over the phone. Families whose children fail the MCHAT-R/F, or whose provider has high suspicion for ASD, are eligible to participate in the remaining components of the study. Families who are not interested in continued participation may opt out of the study. Those who express interest in continuing participation will meet with study staff to learn more about the study and complete informed consent

An additional recruitment strategy will be in place to reach eligible families that were not referred to the study by their child's provider. Research staff who have access to incoming referrals to the DBP clinic, will send a letter to primary care providers of children >= 15 months and =< 27 months who have failed the MCHAT-R/F and/or have been referred to the DBP clinic for a developmental evaluation for concerns related to ASD. The letter will describe the study, who is eligible, how to refer, and seek permission to contact the potentially eligible family. Research assistants will follow up with families whose provider grants permission to screen potentially interested families for eligibility as described above.

At CHOP, an additional step is being put in place for the secondary recruitment strategy per the recommendation of the CHOP IRB and the CHOP clinical staff. For children at CHOP who fail the MCHAT screen at a well-child visit but who are not referred to the CHOP DBP clinic or the study, study staff will first send a letter to the primary care provider (PCP) for permission to contact the family. If the provider grants permission, study staff will then send an opt out letter to the family. CHOP study staff will wait one week after sending the letter to begin calling the family to screen for study eligibility.

At Yale, the research staff does manual chart review to ascertain baseline and ongoing developmental screening rates. As they are reviewing charts to determine screening rates, if they identify a child who failed the MCHAT screen and provider wrote in the note that the family gave permission for the study to contact them, the coordinator will consider that a referral to the study.

9.2 **Consent**

Informed consent will occur in person in a private location selected by the participant. Study staff who have been trained in consenting procedures will obtain informed consent. They will review the consent for/with the participant. They will explain the parent is consenting for his/herself and the child referred for the developmental assessment. In addition, we will use the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR),[66] which our team has used in other studies to determine participants' capacity to give informed consent. The MacCAT-CR has been used widely in clinical research to assess a participant's competence to understand the nature of the study and right to express a choice regarding study participation. Potential participants will be given as much time as needed to answer questions and consider participation. Research staff will explain that the participant does not need to decide about study participation at the time of the first visit and could schedule another visit at a time of their choosing to complete the consent process. Families that do wish to participate will sign the attached consent form.

If guardianship changes during the course of the study, we will offer enrollment in the study to the new guardian. If the new guardian is interested, we will consent her/him and the assigned navigator or care manager will work with him/her for the remainder of the intervention period.

9.3 **Facilitated diagnostic evaluation.**

Families in the CCM group will continue to receive usual care at the DBP Clinic. At BMC, this includes receipt of a parent information packet upon referral; 3 visits to conduct the diagnostic evaluation, visit 1 to obtain child and family history; visit 2 to conduct diagnostic testing, Autism Diagnostic Observation Scale (ADOS-2);[44] and visit 3 to discuss results of the evaluation; and routine telephone appointment reminders prior to visits. Usual care is similar but varies slightly at CHOP and Yale. Consistent with a high-quality medical home, the care manager will be responsible to ensure that the referral for the diagnostic evaluation has been made. She is also available for family-initiated support.

Families in the FN group begin to work one-on-one with the navigator who, in contrast to the conventional care manager, provides off-site support – e.g., home visits or accompanying families to appointments. Within approximately 2 days of informed consent, the family will be contacted by the navigator by phone to arrange the first in-person meeting at a location convenient for the parent. The goal of FN during the diagnostic evaluation period is to ensure timely completion of the evaluation. The exact number and intensity of interactions with the FN is up to the family. The focus of these interactions is to understand the structure and purpose of the evaluation, gather and complete required materials, and address logistic barriers related to the diagnostic visit. Because the navigation model is individualized based on family needs, the actual number and types of visits will vary among participants. Each session should take about 30 minutes.

9.4 **Referral to and engagement in treatment.**

Families in the CCM group. Children who fail the M-CHAT-R/F[65] will be offered referral to community Birth to Three early intervention programs. The care manager will support families as needed with these referrals and will continue to provide family-initiated, clinic-based support to families for up to 100 days after the completion of diagnostic evaluation, if the family contacts the care manager.

Families in the FN group. The navigator will continue to work with the family after the diagnostic evaluation to access recommended services and support the family's engagement in treatment. Referral to specific services and community supports will be determined based on the child's diagnosis and family preferences and needs. Navigators will assist families to resolve logistical barriers and ambivalence to engagement in services. We estimate that families will have 3 face-to-face visits during the 100 days after diagnosis. These visits will be supplemented with, on average, 6 telephone and email contacts.

9.5 **Fidelity.**

To enhance fidelity among FN and decrease the likelihood that CCM will use motivational interviewing (MI) and collaborative problem solving in their interactions with families, we will monitor treatment fidelity by audiotaping randomly selected sessions for each FN and CCM monthly. We will review these audiotapes to assess protocol adherence using standardized checklists that allow us to check for both inclusion of unintended elements and omission of required elements. We have used such checklists in our previous studies. For FN, the checklist will assess MI fidelity by determining the presence of key MI and collaborative problem-solving processes. For CCM, we will look for the inclusion of these same components to monitor for drift/contamination.

9.6 **Follow-up assessment.**

Families will be asked to complete follow-up assessments 3 times during the study period. We collect data on measures of patient-centered outcomes: physical and emotional functioning; stress; caregiver burden and mastery; social support; and coping strategies. Assessments of patient-centered outcomes are timed to key intervention points - diagnostic resolution, termination of navigator services, and 12 months after the date of the failed MCHAT-R/F – in order to assess their role as mediators at these pivotal time points. Research assistants blinded to study allocation will obtain these data through verbal administration in the family's primary language. An instrument comprising the following scales takes an average of 40 minutes to complete.

CLINICAL AND SERVICES OUTCOMES			
Outcome	**Measurement**	**Data Source**	**Timepoints assessed**
Expedited diagnostic evaluation	Achievement of diagnostic resolution Yes/No Children who complete the diagnostic assessment within the 12-month follow-up period Diagnostic interval Number of days Defined as beginning the day of the positive confirmatory screen and ending the day when the family receives a determination (yes/no) of ASD diagnosis.	Medical records	12 months; retrospective chart review
Referral to treatment	Time to receipt of Birth to Three EI services Number of days from failed M-CHAT Time to receipt of ASD services/recommended services Number of days from date of diagnosis	Early intervention records and records from other service providers that provide ASD services	12 months; retrospective record review
Engagement in treatment	Number of hours of services Hours ASD specialty services; Hours related medical services Adequacy of services Yes/No; Based on National Research Council of the National Academies of Science guideline of 25 hours/ week; Absenteeism Number of family-initiated "no show" and cancellations divided by the number of scheduled appointments in the 6-month period following diagnosis	Early intervention records and records from other service providers that provide ASD services	12 months; retrospective record review
Determination of ASD diagnosis	Determination of ASD diagnosis will be based on DSM V criteria made by a Board Certified DBP Pediatrician. Assessments are based on site protocols; all use standardized, validated measures appropriate for very young children. Obtained from medical record review or medical record problem list	Medical records	12 months; retrospective chart review
Satisfaction with ASD-related services	Family satisfaction with care will be measured using the Satisfaction with Hospital Care Questionnaire[61] subscales on information, patient autonomy, and emotional support. been used with ethnically diverse populations.	Parent report	Follow-up interview 100 days post-dx; 12 month follow-up
Satisfaction with Family Navigator	Patient Satisfaction with Interpersonal Relationship with Navigator (PSN-I)[46–48] is a newly validated 9 item scale to assess satisfaction with the interpersonal relationship with the navigator. It demonstrated strong psychometric properties when validated with samples of culturally diverse, underserved cancer patients.	Parent report	Follow-up interview 100 days post-dx
PATIENT-CENTERED OUTCOMES			

Caregiver stress	Perceived Stress Scale- Self-Report (PSS)[49] –Stress domains include unpredictability, lack of control, burden overload, and stressful circumstances. Reliability studies have demonstrated Cronbach alphas between 0.78 and 0.86 in a variety of populations. Evidence of concurrent validity includes positive correlations with inventories of burnout, somatic symptoms, healthcare utilization, and cortisol levels. Parenting Stress Index– Short Form (PSI)[50–52]– The PSI assesses a wide range of parenting behaviors, including attachment to child, social isolation, competence, relationship with partner, and parental health. Cronbach's α for the parent domain is 0.93 and the test-retest coefficient is 0.96.	Parent report	Baseline and all follow-ups
Caregiver burden, and mastery	Brief COPE[53] a valid and reliable 28-item instrument designed to measure parents' coping strategies. Its 3 subscales include problem-focused coping, avoidant coping, and social coping. It will be administered with the Pearlin Mastery Scale[54], a widely used measure of perception of control.	Parent report	Baseline and all follow-ups
Parental Physical/Emotional Health	Veterans RAND 12 item Health Survey.[55] VR-12 includes 12 original question items from the VR-36. The questions in this survey correspond to seven different health domains: general health perceptions, physical functioning, role limitations due to physical and emotional problems, bodily pain, energy/fatigue levels, social functioning and mental health.	Parent report	Baseline and all follow-ups
Social support	Medical Outcomes Survey – Social Support scale.[56] This is a brief, multidimensional, self-administered, social support survey that was developed for patients in the Medical Outcomes Study (MOS), a two-year study of patients with chronic conditions. This survey was designed to be comprehensive in terms of recent thinking about the various dimensions of social support.	Parent report	Baseline and all follow-ups
Child's impact on the family	Family Impact Questionnaire.[57] The FIQ measures parent's perceptions of their child's impact on family functioning.	Parent report	Baseline and all follow-ups
Parenting stress specific to symptoms of autism	Autism Parenting Stress Index.[58] Screening and triage measure for evaluating the parenting system and identifying issues that may lead to problems in the child's or parent's behavior. Focuses on three major domains of stress: child characteristics, parent characteristics and situational/demographic life stress.	Parent report	Baseline and all follow-ups
Child's adaptive functioning	Adaptive Behavior Assessment System II.[59] The ABAS measures functional and adaptive skills overall and on sub-scales including communication, self-direction, and social skills.	Parent report	Baseline and 12 month
COMMON MEASURES REQUESTED BY NIMH			
Family medical history	Autism Centers of Excellence (ACE) Family Medical History. This tool collects information on the health of all family members, including diagnoses such as autism and down syndrome.	Parent report	Baseline
Child's cognitive ability and motor development	Mullen Scales of Early Learning.[62] This tool assesses developmental status in the areas of Visual Reception,	RA-administered	12 month Follow-up

	Fine Motor, Receptive Language, and Expressive Language scales		
ASD diagnostic assessment	Autism Diagnostic Observation Schedule (ADOS-2)[44] The ADOS assesses communication and repeated and restricted behavior to diagnose children with autism spectrum disorder.	Clinician-administered	Developmental Evaluation and 12 month follow up.
Child's adaptive behavior	Vineland Adaptive Behavior Scales (VABS-III).[63] Parent/caregiver report child functioning in the areas of social interactions, communication, and daily living skills.	Parent report	12 month Follow-up

At the third follow up encounter,12 months after the date of the failed MCHAT-R/F, we will ask families to complete measures of service satisfaction and to describe their experience with the diagnostic evaluation and accessing services in their own words. This may take an additional 5-10 minutes, depending on what the family wishes to tell us. With the participant's permission, these comments will be audiotaped. We will also administer the Mullen Scales of Early Learning and the Vineland Adaptive Behavior Scales during the 12 month interview. During this visit we will also ask families to complete a second ADOS (Autism Diagnostic Observation Schedule-2)[44] assessment to track children's stability of symptoms over time. The first ADOS is completed as part of standard care during the child's developmental assessment at the clinic, but an additional ADOS is not part of the standard of care at any of the research sites. This second ADOS will be done about a year after the initial ADOS and may be completed at the clinic or anywhere convenient for the family. We expect the 12 month interviews to take about 3 hours to complete, and we will offer to complete them in one visit or multiple visits depending on the family's preference. If the results on the second ADOS allow families to access additional services for their child, then our study team will work with families to obtain the documentation that will entitle them to these services. Results on the second ADOS will be shared with the child's pediatrician if it shows concern for autism and the child did not receive an autism diagnosis at the time of initial evaluation by the clinic.

Estimated maximum duration for participant families is 12 months, assuming 12 months from the time of the failed MCHAT-R/F to the final outcome assessment.

Additionally, families will be asked to complete a phone call with study staff 3-4 months prior to the final interview. During this call, we will ask families some questions about the child's services. This will allow us to more closely track the child's treatment over the course of the study. The phone call will take approximately 10 minutes. For families who have already consented to the study, we will inform them of this change either at the next planned visit or by phone. The date and details of these conversations will be documented in study participants' files.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 **Definitions**

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that
(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:
- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:
- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 **Safety Review**

Both the risks listed in Section 6.1 and unknown risks will be monitored as follows:

Throughout the course of the study, all procedures and staff conduct will be monitored on an ongoing basis by each site PI (Dr. Bennett for CHOP; Dr. Weitzman for Yale; and Dr. Feinberg for BMC). Data concerning the participant accrual process, baseline characteristics of enrolled participant, degree of parental stress and diagnosis status of the children will be monitored on a weekly basis. Investigators will meet weekly with intervention providers and research assistants to discuss all active study participants.

Monitoring will pay particular attention to adverse events or events that have the potential to become adverse. Adverse events for this study will include mandatory reports to child protective services for suspected abuse or neglect, new (i.e. previously unknown) domestic violence situations, complaints from study participants, or any instance of breach of privacy or confidentiality. Reporting of adverse events and unanticipated problems to the IRB at each site will be done by the study team for that site and occur in compliance with the IRB reporting policies for that institution. Additionally, any unanticipated problems and adverse events will be reported to the study's Data Safety Monitoring Board (DSMB), which will meet every six months during the project period.

Dr. Cabral (statistician) will join the site PI monthly telephone calls quarterly to review data for the overall project. In case of an unanticipated problem or adverse event, site PIs will notify Dr. Feinberg concurrent with notifying his/her home institution's IRB. If central monitoring uncovers an unanticipated problem based on review of the aggregate data, then Dr. Feinberg will alert the site PIs of the issue, as well as the Boston University Medical Center IRB.

Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.3 **Stopping Rules**

The study has no stopping rules.

11 Data Handling and Record Keeping

11.1 **Confidentiality**

- Participants' names will not be put on their respective research surveys or data collections forms. Rather, participants will be assigned a code number (subject ID). The list that links this code number and the name will be kept in a separate, locked location.

Only study personnel will have access to this information. Additional steps will be taken to protect the privacy of all participants. These include separating all research interviews with the assigned code number from all referral documents including the participant's name and contact information, which will also be kept in a locked location.

- Audiotapes that are obtained as part of the research will be identified by subject ID and stored in a password protected location on a HIPAA-compliant web storage system to which only the study PI and key study staff have access to. They will be destroyed after 3 years. Transcribed audiotapes will be stripped of all identifiers and stored on a password protected computer in a password protected file.

- All family navigator sessions will take place in a private area where the parent feels comfortable. If family navigator personnel accompany a parent to an appointment, verbal permission to attend will be received from the parents by the family navigator before this type of session.

- All research interviews, including baseline and follow up measures will be completed in a private office or setting

Access to individually identified private information. Only the PI and research staff that have been trained on HIPPA regulations and human subjects protection will have access to individually identifiable information about human subjects. This information will only be available after participants have consented to study participation or have specifically awarded permission to this information

11.2 **Source Documents**

Material to be collected. For this study, we will make no use of biological specimens. We will gather the following types of data:

- Individual participant data will be collected directly and voluntarily from the participants themselves in the form of confidential paper data collection instruments and face-to-face interviews. These data will be collected from participants in qualitative interviews and from families who provide informed consent.

- Diagnostic and service data will be abstracted from the medical, early intervention, and ASD service provider records of children whose families have provided consent.

11.3 **Study Records Retention**

All subjects will be assigned a subject ID. This study code will be marked on each study document, or survey associated with the subject. A cross-walk that links study codes to subject's names will be kept in a password protected file on a password protected computer at each site in a locked office. Each site will only have access to identifying information for subjects from their site, except for the central research team in Boston who will manage data quality across all sites. This cross-walk will be kept throughout the duration of the study, and then destroyed once data analysis is complete.

All hard copies of the data will be kept in a locked file cabinet in a locked office. Data will be kept for 3 years after study completion as required. After the period all paper records will be destroyed by shredding.

All data entered for analysis will be entered into a password protected database (StudyTRAX) and kept in a locked office. Database files contain different levels of permission to ensure several layers of protection. The database application, called StudyTRAX, uses MS SQL Server as the back end relational database. The program can support one or more research studies, is presently being used at dozens of major academic research centers to support numerous NIH funded projects and is available commercially. The HIPAA privacy rules and HIPAA security rules mandate that covered entities have in place appropriate policies and procedures to protect the confidentiality and security of protected health information. In compliance with these regulations, the database security features of StudyTRAX target multiple levels including the data element (e.g., restricted access to fields), user (e.g., password authentication access), application (e.g., role-based access to features, access audit trails), and hosting services (e.g., firewall, secure sockets layer). Taken together, these features ensure access control, audit control, data integrity, user authentication, and transmission security. The research project(s) will be set up in StudyTRAX to ensure exported datasets are de-identified as defined in the HIPAA privacy regulation [45 C.F.R. §164.514 (b)(2)].

Data security is assured by the following: (1) All server requests are transmitted over SSL using 256-bit encryption, (2) a dedicated Cisco router firewall only allows requests to StudyTRAX, (3) the database is stored on a separate server in a private independent subnet with no public IP address, (4) database and log files are encrypted, and (5) database and log backups are encrypted.

Data is protected from loss by the following: (1) A redundant array of independent disk [RAID] Level 5 is used to ensure that data will not be lost if a hard drive fails, (2) full database backups are done nightly, (3) database log file backups are done every 15 minutes, (3) database integrity checks and index maintenance are performed nightly, (4) the database and log backup files are retained as part of Rackspace's backup process and also transferred every hour to Microsoft's Azure geographically redundant storage.

12 Statistical Plan

12.1 **Study Hypotheses**

12.1.1 Primary Hypothesis.

- We hypothesize that relative to CCM, children whose families receive FN will achieve diagnostic ascertainment and engagement in recommended developmental service in fewer days than children whose families are assigned to CCM.

12.1.2 Secondary Hypotheses

- We hypothesize that FN will have a differential effect at the three study sites
- We hypothesize that race and ethnicity will moderate the effect of FN
- We hypothesize that parents who receive FN will experience lower caregiver stress, burden, and family impact that parents who receive CCM

12.2 **Sample Size Determination**

We plan to enroll and randomize approximately 250 children who are our primary recruitment sample per clinicaltrials.gov. Additional NIMH funding for a supplement (R01MH104355-04S1) awarded September 16, 2017, supports the recruitment of an additional 100 children that will allow the subgroup analyses as outlined below. According to Kraemer's threshold of clinical significance[38] concept, we estimate the required sample size to detect the smallest differences in primary outcomes that are of clinical importance. In the ITT analysis, we assess the adequacy of the expected sample to detect main effects among all children randomized (125 per treatment arm), assuming a two-sided alpha of 0.05. The augmented sample size (350) gives us sufficient power to conduct subgroup analyses to detect differences in key outcomes by race and gender. Specifically, this is a sufficient sample to detect a 20% difference in diagnostic completion rates by gender. Similarly, the sample size allows the detection of moderate effect sizes for patient-centered continuous outcomes, such as social support. We present power calculations for planned categorical analyses. Power to detect between group differences in analyses of count data will exceed those presented below.

Completion of diagnostic evaluation. We consider a 25% absolute difference in diagnostic ascertainment rates between treatment arms to be clinically meaningful and to provide evidence of the effectiveness of FN compared to CCM. Based on pilot studies (now published),[67,68] assuming that 65% in the CCM arm would achieve diagnostic ascertainment and a moderate design effect resulting from site clustering (intraclass correlation of 0.01), a sample size of 250 was estimated to detect 25% difference in diagnostic ascertainment with 80% power at a two-sided alpha of 0.05.

Time to receipt of recommended services. We assume that 80% in FN arm and 60% in the CCM arm will receive ASD services 5 months after a failed M-CHAT screen. A log rank test will have over 80% power to detect such differences as clinically significant at the 0.05 level.

12.3 **Statistical Methods**

12.3.1 Logistics.

We will record the numbers of families eligible and refusing participation. We will assess reasons for refusal at each stage of the protocol and record participant attrition. We will note all adverse events.

12.3.2 Intervention main effects.

Under the direction of Dr. Cabral, we will conduct an intention-to-treat (ITT) analysis.[69] In the intention-to-treat analyses, the denominator will include all children randomized to a treatment arm.

- For categorical outcomes – we will use logistic regression models to compare the proportion of children who were referred for diagnostic evaluation, completed the diagnostic evaluation, and received recommended ASD specific services.
- For time-to-event outcomes –time to diagnostic resolution, and time to receipt of ASD services - we will use censored analyses to construct Kaplan-Meier curves of time to event, and estimate hazard ratios, using Cox proportional hazard models.

12.4 **Mediator/ Moderator Analyses**

Moderation analyses Using Rothman's methodology,[70] we have identified two a priori, theory-based potential effect modifiers: site and child race/ethnicity. To assess effect modification by site we will include group x site interaction terms in our statistical models; to assess for effect modification by race/ethnicity we will include a group x ethnicity interaction term in these models. If the interaction is significant, we will perform stratified analyses to identify the nature of such moderation.

Center effects. One of the strengths of our study is that each clinic site (center) is unique – in terms of its own clinical processes and the early intervention sites it has access to. We will pay close attention to center effects. By randomizing our sample separately within each center, we eliminate the potential of confounding by center. However, we will also examine potential clustering and assess effect modification by center,[71] which will help us determine the generalizability of the FN model.

Racial and ethnic group effects. Specific barriers to ASD identification and service provision differ by race and ethnicity.[22,25–28] A strength of our sample is that we can examine the impact of the intervention for key population subgroups that have been under-screened, -assessed, and -treated for ASD.

Examination of intervention mechanism. Given our intervention's emphasis on goal setting and action planning, decreased caregiver burden, decreased perceptions of stress, and behavioral activation constitute likely intervention mediators. We will examine mediational effects using two different, but related, methods: the approach of Baron and Kenny[72] and the use of path analysis models. Each of these approaches can be used to differentiate between direct and indirect intervention effects. In the path analysis models, we will compare the fit of meditational vs. non-mediational models by differences in Akaike's Information Criterion, the comparative fit index (optimal value > 0.95), the Tucker-Lewis index (optimal value > 0.95), and the root mean square error of approximation (optimal values < 0.06). We will fit these models with MPlus software, which allows for the modeling of measurement and dichotomous, endogenous and exogenous variables.

12.5 **Sub-group Analyses**

Per clinicaltrials.gov, data from 250 enrolled participants will be utilized to measure primary outcomes as outlined above. An additional sample of approximately 100 participants will facilitate subgroup analyses by gender, race, and ethnicity. The sample size of approximately 350 participants provides sufficient power to detect key differences in outcomes by gender and race/ethnicity. Proposed sub-group analyses are as follows:

- *Relative to ASD screening*: We will examine differences in our baseline data stratified by gender, race, and ethnicity to understand differences among children identified with ASD risk through routine screening in primary care. Key variables of interest are age at positive screen, MCHAT-R/F score, adaptive functioning, and measures family functioning and parental stress.
- *Relative to diagnostic ascertainment and engagement in service*. We will examine gender and racial/ethnic differences between the proportion of children who complete the diagnostic evaluation using logistic regression models. We will also assess differences in time to diagnostic resolution, and time to receipt of ASD services using censored analyses to construct Kaplan-Meier curves of time to event, and estimating hazard ratios from Cox proportional hazard models. Among children who receive an ASD diagnosis we can examine gender and racial/ethnic differences in engagement in

services through analysis of early intervention and autism specialty service records that detail recommended hours of service and hours of service received.

- *Relative to trajectories of family functioning over time.* We will compare the effect of gender and race/ethnicity on measures of family/parental functioning (parenting stress, social support, mental health) among young children diagnosed with ASD. We will use multivariate models for longitudinal data (here, for measures taken at baseline, and three additional time points during the follow-up period) that account for the correlated nature of the data. Specifically, we will employ linear regression models fitted via generalized estimating equations (GEE) or mixed models. These models permit the inclusion time-dependent variables, which allow us to examine, for example, the effect of child's adaptive functioning on parent trajectories. In these models, we will adjust for any differences in baseline characteristics between gender groups. We will assess for effect modification by gender by assessing the significance of the group by time by gender interaction.

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

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