Title: Intensive Intervention for Toddlers with Autism

ClinicalTrials.gov NCT ID: NCT00698997

Document: Protocol

Date: January 18, 2019

DESCRIPTION OF STUDY

Principal Investigator: Sally Rogers Ph.D.
Title of Study: **Intensive Intervention for Toddlers with Autism**

PURPOSE AND PROCEDURES:

This is a multi-site, investigator-initiated, phase IIII clinical trial. Funding has been obtained from the NIH.

2. Describe the specific aims of the study, research methods and procedures.

SPECIFIC AIMS

Autism is a complex and pervasive disorder with often devastating effects on social, cognitive, and language development. As many as 50% of persons with autism meet criteria for mental retardation. A large minority does not develop complex, communicative speech (Rutter, 1978). The presence of both mental retardation and lack of speech are associated with very poor outcomes in autism (Gillberg, 1991); (Lotter, 1974). The verbal level that children attain during the preschool years is a strong predictor of adult levels of adaptive skills and educational level (Venter, Lord, & Schopler, 1992).

There is evidence that intensive intervention early in life can improve the development of useful speech and decrease the severity of mental retardation. Several groups have indicated that 75-95% of children receiving very intensive and carefully constructed early intervention develop useful speech by age 5 (Lovaas, 1987); (McGee, Morrier, & Daly T., 1999); for a review see (Rogers, 1998). Three separate groups have now reported that a significant proportion of children receiving intensive intervention early in life make outstanding progress, with autism symptoms diminishing and developmental outcomes improving such that these children no longer have evidence of disability (McEachin, Smith, & Lovaas, 1993); (Sallows & Graupner, 2005); (Howard, Sparkman, Cohen, Green, & Stanislaw, 2005)

Thanks to the development of better diagnostic tools and a greater level of professional education, autism is being identified in two year olds and in even younger children, with such early diagnosis justified by the rationale that the earlier intervention begins, the better the outcomes may be. However, there are no published outcome data on intervention models or effectiveness for children who begin intervention by or before 24 months. Furthermore, some teaching procedures considered appropriate for older children, (e.g., 40 hours per week of adult-directed intervention, much repetitive practice while sitting at a table (Lovaas, 2002), 1987) are considered developmentally inappropriate for toddlers (Sandall, McLean, & Smith, 2000).

Dawson and Rogers have implemented a feasibility study of an intervention designed for toddlers with autism using a randomized controlled design. The approach involves a relationship-based frame to accomplish developmentally based objectives using naturalistic application of applied behavior analytic principles. The approach fuses the Denver Model (Rogers, Hall, Osaki, Reaven, & Herbison, 2000) and Pivotal Response Training (Koegel, Koegel, & Carter, 1999), and is delivered 1:1 for 25 or more hours per week to 24 toddlers with autism for a two year period. The contrast group receives standard community based intervention. Preliminary results demonstrate large and significant group effects after only 12 months and considerable variability of intervention outcomes in both groups.

Goals of the current project: The proposed, multisided randomized clinical trial (RCT) draws from this, and other previous studies of early intervention in young children to answer two questions: (1) Does this experimental intervention for toddlers with autism reduce disability associated with autism significantly more than standard community interventions?; and (2) What environmental, child, and biological characteristics mediate and moderate intervention response and outcomes at age 4?

We will address these questions through the following Specific Aims:

Specific Aim 1: To conduct a multi-site intent-to-treat randomized control trial of early intensive behavioral intervention (Early Start Denver Model) compared to standard community intervention involving 108 toddlers with autism (12-24 months of age), 36 at each of three sites, to evaluate the efficacy of very early intervention for improving child outcomes after 12 and 24 months of intervention, based on measures of cognitive, language, and social behavior and severity of autism symptoms;

Specific Aim 2: To examine the efficacy of the Early Start Denver Model parent intervention for optimizing parent interaction strategies and improving parental quality of life;

Specific Aim 3: To examine predictors, mediators, and moderators of outcomes for children in both groups, with variables involving social environmental risks and protective features, individual child risk or protective features, and biological risks and protective features.

Overview of the research design.

This is a multi-site intent-to-treat randomized controlled trial of the Early Start Denver Model across three different geographic sites. 108 subjects will be randomized into experimental or community availability intervention groups. Three clinical sites recruit, assess, and treat 36 subjects each. Children ages 12-24 months are recruited, stratified by DQ, and randomized to community or experimental interventions. The experimental group will participate in two phased intervention that lasts for approximately 28 months. They will first receive a 12 week intervention including 12 weekly 1 to 1.5 hour sessions at the MIND Institute focused on teaching and coaching parents to deliver the intervention throughout natural daily caretaking routines and play periods with their child. The community intervention group will receive a parent education kit (e.g. Autism Speaks 100 day kit) appropriate for parents of newly diagnosed children with autism. All families receive four comprehensive assessments across the enrollment period; in addition their development will be monitored every six months using the Vineland Adaptive Behavior Scales. Every 6 months after participants' 4th and final assessments, a graduate student researcher calls each family to check in and collect the Vineland Adaptive Behavior Scales-II (Parent/Caregiver Rating Form) and an updated intervention history. Children in the community group are referred to their community resources. Children and families assigned to the Early Start Denver Model intervention will first complete a 12 week parent coaching course and then will receive 25 or more hours per week (20 from the project staff and 5 from the parents) of individual intervention delivered in their homes for 24 months, 50 weeks per year, with curriculum assessment and revision every 3 months. Parents continue to receive 1.5 hours of training biweekly, incorporating the Early Start Denver Model teaching approach to their ongoing family activities and routines, and also individually targeted interventions using functional assessment and intervention (e.g. toilet training, sleep problems, tantrum reduction). Interventionists' and parents' fidelity to intervention procedures is monitored throughout intervention. Potential variables that may serve as mediators or moderators of (1) response to intervention, and (2) outcomes at age 4 will be examined in both groups of children, including social- environmental risks and protective features, individual child characteristics, and biological risks and protective features. These will be examined using structural equation models combining all 108 subjects. Annual evaluations will be carried out until the end of the study.

This is an **intent-to-treat design**, in which all children enrolled in the study will be followed through the entire course of the study, whether or not they continue to receive the experimental intervention. All children's data will be included in the original assignment group regardless of their intervention course after enrollment. Thus, the potential for subject attrition and replacement (particularly for families whose children may not do well and who may withdraw from intervention) to confound outcomes will be protected against through this aspect of the design.

Description of the experimental intervention

Intervention delivery.

The first phase of the intervention includes 12 weekly 1 to 1.5 hour sessions focused on teaching and coaching parents to deliver the intervention throughout natural daily caretaking routines and play periods with their child. Parents will be taught and coached on one aspect of the intervention each week in the clinic session, and then will practice it at home daily in natural family routines and play activities. Following the first phase, each child in the experimental intervention will receive 25 hours a week of the experimental intervention in their homes, delivered individually, for 50 weeks per year, for two years. Twenty hours per week will be delivered by trained interventionists, and 5 hours per week will be delivered by the trained parents. Interventionists will provide 10 two hour teaching episodes involving play activities per week in the home. Parents will continue to deliver the intervention in natural family routines and play activities. In addition, each child will receive additional services through public birth to three services, or other therapies that the parents may choose, for several more hours per week.

Intervention Team. The interdisciplinary Intervention Team includes fully credentialed and very experienced professionals including a speech/language pathologist, behavior analyst, OT, and a clinical psychologist, each responsible for the disciplinary-related aspects of the child's intervention. The team is headed by a clinical psychologist, the Treatment Team Coordinator. Additionally, each site will have a pediatrician available for consultation. This team meets biweekly to review child progress and shares responsibility for overseeing the child's intervention, consulting, and problem solving on all aspects of the intervention. The Project PI in each site is a licensed psychologist and is part of this team.

The daily planning and delivery of each child's intervention will be the responsibility of an Intervention Team Leader, who is supervised by the Treatment Team Coordinator. Team Leaders are very experienced fully credentialed professionals in the field of early intervention: behavioral or clinical psychology, or early childhood special education. The Team Leaders supervise the interventionists who deliver the intervention in

the children's homes. Interventionists have a Bachelor's degree in education or related field and have some experience with either young children or with children with autism. Before beginning to provide the intervention to the children, the interventionists will participate in one or more months of full-time training provided by the Training Coordinator, including didactic readings, homework, observations, hand-on training, and in vivo observation of intervention with current participants in the study. Interventionists can work independently with children once they have met rigorous clinical competency criteria. Interventionists meet weekly for case conferences with their Team Leaders and are observed regularly to assess on-going clinical competence and intervention fidelity. They are also videotaped regularly and their tapes are assessed for intervention fidelity. All clinical activities are supervised by the Treatment Team Coordinator.

The experimental intervention. The intervention to be delivered is the Early Start Denver Model (Smith, Rogers, & Dawson, 2006) available in the Appendices). The ESDM is based on a fusion of two well known approaches: (1) the Denver Model, a comprehensive intensive early intervention for preschool age children with autism originally developed by Rogers and colleagues, (Rogers et al., 2000), and (2) Pivotal Response Training (PRT). Pivotal Response Training (PRT) involves naturalistic delivery of intervention derived from applied behavior analysis. PRT was developed by Schreibman and Koegel in the 1970's. It involves a naturalistic application of applied behavior analysis to develop language and social skills and has extensive empirical support developed by Laura Schreibman and Robert Koegel in the 1970's and 80's (Koegel, Koegel, & Surratt, 1992); (Koegel, O'Dell, & Dunlap, 1988); (Schreibman & Pierce, 1993).

The Early Start Denver Model was developed to address the unique needs of toddlers with autism, and incorporates existing techniques that have received empirical support for improving skill acquisition in preschoolers with autism. The intervention is provided in a toddler's natural environment, the home. This intervention is offered at high intensity (e.g., 25 or more hours per week), consistent with the National Research Council's (2001) recommendation for intervention for children with autism within this age range.

The individual intervention plan: teaching content. Each child's plan is defined by (1) **a set of short term objectives** that represent what is to be taught over a 12 week period, and (2) **a set of activities** carried out daily to teach the objectives. The objectives are derived from assessment on a curriculum tool, The Early Start Denver Model Curriculum Checklist (pp70-89 in the Manual, included in the Appendices). The Curriculum Checklist covers the following 10 domains: receptive communication, expressive communication, social interaction, imitation skills, cognitive skills, play skills, fine motor skills, gross motor skill, independence/behavior, and joint attention. The Checklist contains approximately 500 items covering the age period from approximately 9-12 months to approximately 48-60 months. The items are grouped by domains, developmentally sequenced within domains, and are further subdivided into four developmental levels, with Level 1 roughly representing 12-18 months, Level 2 18-24 months, Level 3, 24-36 months, and Level 4 36-48 months.

A **curriculum assessment** occurs at the start of the first phase or parent coaching phase and every 12 weeks afterwards, to develop the intervention objectives that frame the intervention for the next 12 weeks. The Team Leader, parent, and child complete the assessment using direct observation, probes, and parent report of skills and parent intervention goals. During the assessment, the Team Leader probes all of the items in a particular level, using direct assessment, parent report, and therapy assistant reports. Each item is scored pass, emerging or inconsistent, or fail. Based on the first failed or inconsistent passes, two to three objectives are written for each developmental domain, so the child has 25 or so objectives per quarter.

These **Quarterly Intervention Objectives** define the child's intervention for the next 12 weeks. They are written in an A-B-C format: specifying the antecedent condition in which the target behavior will occur, the operational definition of the behavior involved in the targeted skill, and the criteria to determine mastery. Mastery of an objective typically involves spontaneous performance of the targeted skill in multiple appropriate contexts and generalization of the skill across multiple settings or people. Thus, generalization is built into every single objective.

Each quarterly objective is then task analyzed into a sequence of **teaching steps**. The child's current baseline skill on each objective is indicated as the "maintenance" or current level of skill performance on that objective, and the next step on the task analysis becomes the immediate teaching goal for that objective. These teaching steps for each objective are condensed on a **daily data sheet.** Performance data are gathered throughout the therapy session in 15 minute intervals.

Children generally achieve 75-90% of their objectives each quarter. If an objective is not achieved during the quarter, its continued appropriateness is reconsidered. If a child has been making good progress on it, it will likely be continued into the next quarter. If the objective seems poorly chosen or unusually difficult, it may be dropped for a quarter or two. Interventionists are trained in the use of the data system during their initial

training, and rater reliability on the data collection system is collected quarterly by the Treatment Team Coordinator and Fidelity Coordinator. The Team Leader reviews the data weekly and updates the data sheet for the coming week as needed, based on the child's performance data from the past week.

Teaching procedures: teaching process. There are both general and specific aspects to the teaching process. **General aspects of the teaching process,** quantified in the **ESDM Fidelity Tool (**available in the Treatment Manual on page 308-322), involve the use of varied, naturalistic, child-initiated activities in which to embed instruction, based on the empirically demonstrated gains in spontaneity, motivation, maintenance, and generalization that this kind of teaching supports for skills in which there are intrinsic reinforcers (Koegel et al., 1992; Koegel, Koegel, Hurley, & Frea, 1992). These are specified in the fifteen teaching behaviors assessed on the fidelity tool. Adults freely choose materials and activities in which to teach the targeted objectives to maximize attention and motivation, while considering the child's preferences and learning style.

Tailoring, or individualizing the intervention. A systematic decision process is used to tailor the intervention, by systematically altering teaching procedures to improve progress if children are not progressing rapidly. While the teaching process favors naturalistic teaching, varied activities, intrinsic reinforcers, and shared control, no empirically supported teaching approach is "off limits". The ESDM model requires that teaching procedures be systematically altered by addressing one of three variables if children are not progressing on their targeted teaching step within three to five days or six to 10 therapy sessions. The three variables are: (1) the strength of the reinforcement; (2) the structure of the teaching approach, and (3) the use of visual or augmentative supports. Each variable contains a hierarchy of steps to be followed in order, with each change incorporated for at least 3 days. If no progress occurs, then the next step of the hierarchy is implemented. If progress occurs, then the teaching procedure continues at the same level until all the teaching steps for that objective are mastered. Tailoring the intervention thus involves following a decision tree, presented in the Intervention manual in the Intervention Manual in the Appendix, page 39. This decision tree allows for the entire "toolbox" of teaching practices demonstrated to be effective for children with autism to be used if needed, but it prescribes **how** and **when** to alter teaching processes.

Individual session structure. Once the clinic based parent coaching sessions have been completed, the Early Start Denver Model is delivered in the child's home for 20 hours per week of individual intervention. Interventionists work individually with the child for 2 hour sessions, typically twice a day, 5 days a week (therapy can begin with 1.5 hour sessions for the first month or so if longer sessions appear unhelpful for children. After the first month, enough activities have been built up to fill the 2 hour period). Individual sessions follow a typical structure. The session begins and ends with a greeting routine during which the child and assistant transition to the therapy space, greet and sing a song, change clothes (e.g., take off shoes, put on slippers). Then the two engage in joint activity routines which alternate between object-based routines and sensory social routines. The interventionist maximizes child motivation and attention by varying the activities between the table and the floor, between quiet and active episodes. Learning opportunities occur approximately every 10–15 seconds during intervention interactions, based on our fidelity studies. Transitions between activities are responsive to children's needs for a change and are carried out in a thoughtful and organized fashion that fosters child independence, motivation, and choice. During a transition, children move towards an interesting activity rather than being led or directed to a bare space and waiting for an activity to be presented. Each 15 minutes, the assistant lets the child continue to play with materials for 1-2 minutes while he/she records data on the data sheet. After the first hour, the adult may move to a different part of the house, to offer a snack, or a few minutes of outdoor play. Intervention objectives continue to be addressed during these breaks.

Joint activity routines. Joint activity routines (Ratner & Bruner, 1978) are the vehicle for teaching. (See the Treatment manual [Appendix] for further definitions and examples of the types of joint activity routines used in this intervention). A joint activity routine involves a series of interactions between child and adult that allow for a shared activity to be begun, developed, elaborated, and completed. Inside a joint activity, objectives from at least two different developmental domains are taught. A joint activity routine typically lasts from two to five minutes and involves multiple acts from both therapist and child. The activities are generally chosen by the child, though the adult may offer choices, and the child's initial choice and the adult response to that choice mark the first "round" of interaction in the activity routine. The materials used are typical playthings, not adult-constructed materials, and generally involve several pieces and several different actions, in order to foster multiple communicative rounds, imitative rounds, and increasing cognitive complexity as the activity develops through theme and variation. The toys may be the child's toys at home, or toys brought in by the adult for the intervention session. Both are always available. In this format, interspersal of mastered activities and learning objectives is easy to accomplish and maximizes motivation and interest. As child interest wanes, cleanup

occurs; involving more rounds on interaction, and a new choice is made, beginning the next joint activity routine.

Role of the family. Parents are an integral part of the intervention and are trained and coached in the model as the first phase of the intervention; throughout the enrollment parents have input into objectives, curriculum, and teaching practices. Parents are part of all assessments and their input is sought on all objective and goal setting meetings. During the initial 12 weeks of enrollment in the intervention arm, parents and child together receive 1 – 1.5 hours of intervention in the clinic as the parents learn the intervention model. In the intensive phase of the study, parents continue to receive parent education sessions with their Team Leader in a two hour visit with their child every two weeks in the clinic throughout their enrollment to build their skills in incorporating the Early Start Denver Model approach in their natural caretaking and family routines as well as play activities throughout the day with their child. Additionally, individual difficulties are addressed using functional behavioral assessment and positive behavior support strategies, for behavior problems and for self care development. The goal of parent coaching is to continue to empower parents via skill acquisition, to continue to promote a positive parent-child relationship and continue a sense of parent competency, and to generalize the skills the child has acquired in intervention to everyday family activities. During children's home intervention sessions, parents may be participating, or observing, or attending to other activities in their home. For children receiving care outside the home, intervention may be delivered in alternative setting as long as there is a separate space with appropriate furnishings. Additional caretakers may also be taught intervention techniques.

Use of outside services. Families may remain in the intervention as they pursue any community services they desire for their child, other than additional intensive behavioral intervention from another provider. During the intake phase of the project, both experimental and comparison families are provided with referrals for their local Birth-to-Three Programs, medical professionals, as well as occupational and physical therapists. Supervisors share the intervention objectives with outside intervention providers to coordinate care, and conduct team meetings with other agencies on a quarterly basis to communicate regarding the child's progress. As each child approaches three years of age, intervention supervisors meet with the family to discuss options for participation in preschool. Typically, families will enroll their child in a specialized preschool in their local school district. Supervisor-level intervention staff may provide consultation to the preschool team to support coordination of intervention. The community service component is handled the same in the experimental and comparison groups. Thus, the community service is a constant across the groups; the Early Start Denver Model is added in the experimental group.

3. If applicable, address how the study will involve the use of drugs, devices, biologics, or radioactive materials (both FDA approved or investigational).*

N/A

4. Address if therapeutically removed tissue will be collected, what types, and for what purposes.

N/A

5. Specify the nature, frequency and duration of tests, if any.

   Children will be tested annually, before, during, and after intervention. They will receive a battery of tests, including:

The qualifying evaluation. Three types of assessments will be used in this study**: (1) the qualifying evaluation,** which determines the child's eligibility for the study in terms of the inclusion/exclusion criteria, (2) the measurement of the **dependent variable**—outcomes, and (3) measurement of the **potential mediating and moderating, independent variables**. The qualifying battery and the independent measures will be administered at the point of intake only. Dependent variables will be measured annually using a standardized battery. The qualifying battery will be carried out after the telephone **screening battery** which will consist of the following measures:

(**1) Early Screening of Autistic Traits Questionnaire** (ESAT; Swinkels et al, 2006) will be used for children 12-18 months when first referred. The ESAT is an examiner administered parent interview involving fourteen behaviors that have distinguished infants who later develop autism from others in previous autism studies. The tool has been tested in several studies, including a recent population based study of 31,000 14-15 month old children in the Netherlands. The tool identified no false-positives and 18 infants who were diagnosed with

autism at age 2. This will be used as an inclusion instrument only, to examine parental observations of autism-related behaviors.

(2) Communication and Symbolic Behavior Scales Infant Toddler Checklist (CSBS-DP ITC; Wetherby and Prizant, 2002) will be used for all children when first referred to the project. The CSBS Checklist is a 24 question parent observation interview used to help identify toddlers at risk for developing autism. The ITC has an identification rate of 5/1000 for toddlers with autism, which closely approximates the general population rate of 6/1000. It is designed specifically to help determine whether to refer at risk infants and toddlers for further autism specific evaluation. Psychometric properties include both specificity and sensitivity at 85% and above, a false negative rate under 5% and a false positive rate under 20%. The ITC will be used as a screening tool to increase the probability of identifying toddlers at risk for developing autism.

(3) Modified Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, & Barton, 1999) will be used for children 18-24 months when first referred to the project. The M-CHAT is designed to screen for Autism Spectrum Disorders in toddlers (i.e., over the age of 12 months, and ideally over the age of 18 months to 24 months of age). The M-CHAT is a very useful clinical tool comprised of 23 items that has excellent sensitivity and specificity. The M-CHAT does not require clinician observation. Children who fail 3 items total or 2 critical items will be considered having failed this screen. At the time of referral, each child will be screened on two different autism screeners. Children who meet criteria for autism risk on BOTH instruments will be scheduled for an assessment visit to determine whether they qualify for the study.

The **qualifying** battery will be comprised of the following measures:

(1) Toddler Autism Diagnostic Observation Scale (Lord, Rutter, DiLavore & Risi, unpublished) takes 20 minutes with a child. This is a semi-structured observational assessment that provides a number of opportunities for interaction (e.g., play, turn-taking games, looking at books, etc.) and measures social and communicative behaviors diagnostic of autism. Each item is scored from 0 (typical for age or not autistic in quality) to 3 (unquestionably abnormal and autistic in quality). Scores of 2 and 3 are collapsed and then summed for particularly sensitive items, providing empirically-derived algorithms for both Autistic Disorder (cutoff=12) and Autism Spectrum Disorder (cutoff=7). When the full range of scores from 0 to 3 are summed, they can provide an alternate index of severity (Gotham et al., in press and available in Appendix). All lab personnel will be trained to 80% reliability on the full range of scores to generate severity scores. All sites have established reliability with Dr. Lord previously. Dr. Lord's team will assess ongoing cross-site reliability on this measure and train as needed to maintain reliability. Inter-observer reliability at individual sites will be assessed on at least 20% of interviews after competency has been established. Variables of interest: algorithm scores. The ADOS-T will be used at all 4 assessment points.

(2) Toddler Autism Diagnostic Interview (Rutter, LeCouteur, and Lord 2005, unpublished). The TADI-R is a comprehensive, 2.5-hour parent interview that assesses symptoms in three main areas: social, communication, and restricted activities, as well as providing information concerning early history. The TADI-R provides an algorithm with cut-off scores for autism and has been shown to have excellent reliability and validity (Lord, Rutter, & Le Couteur, 1994), and will be administered to the primary caregiver of the child during a home visit by a trained, reliable administrator. All sites have established reliability with Dr. Lord previously and Dr. Lord's team will assess ongoing cross-site reliability on this measure and train as needed to maintain reliability. Interobserver reliability at individual sites will be assessed on at least 20% of interviews after competency has been established. Variables of interest: algorithm scores. The T-ADI will be used at time points 2 and 4.

(3) Mullen Scales of Early Learning (Mullen, 1995)**.** This is a standardized, normed developmental assessment for children aged birth through 68 months. It provides an overall index of ability, the Early Learning Composite and subscale scores of Receptive Language, Expressive Language, Visual Reception, and Fine Motor skill. For this study, the Mullen will serve two purposes. First, it will be used to generate the variables of interest: the two ratio DQ scores, overall DQ and nonverbal DQ, to characterize the sample at intake. Second, it will be administered annually to examine changes in full scale and nonverbal mental age equivalents. 20% of the assessments will be scored by two raters for reliability checks. The scales take less than an hour to administer. The MSEL will be used at all 4 assessment points. If a child obtains no ceiling on the Mullen (which may occur as children receive their final assessments) we will also give the **Differential Abilities Scale.** The **(4) Differential Abilities Scale** (DAS; (Elliott, 1990) is a standardized test of intelligence with versions suitable for children from ages 2 ½ to 18 years. It examines both verbal and nonverbal performance and provides age equivalents and standard scores. The DAS can be administered to children who are not verbal and it is expected that most children will obtain basal scores on the DAS - if not on the School-age

version, then on the preschool version. It will only be used for children who do not establish a ceiling on the MSEL.

(5)DSM-IV checklist: The **Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision** (DSM-IV-TR), published by the American Psychiatric Association (APA) includes diagnostic criteria for all mental health disorders that are currently recognized. The DSM IV checklist utilizes the DSMIV criteria for Autism Spectrum Disorders. All children who are diagnosed with an ASD also meet full DSMIV criteria across 3 dimensions: repetitive behaviors, language and communication difficulties.

Measurement of the dependent variable – Outcome status. The following will be administered at various time points throughout the years of the study, depending on the variable measured: Time Point (TP)1, at intake; TP 2, is at the end of the first 12 week parent training phase; TP 3, is at the end of 12 months of intensive home based intervention, and TP 4, is at the end of 24 months of intensive home based intervention. Measures are administered at all 4 time points unless otherwise specified.

Developmental measures

(1) Preschool Language Scale, 4th Edition (Zimmerman, Steiner, & Pond, 2002). (Less than 1 hour). The PLS is a standardized assessment of language functioning for children from birth to age 83 months. The two subscales, Auditory Comprehension and Expressive Communication, evaluate how much language a child understands and how well a child communicates with others. The test was recently re-standardized on a representative U.S. sample. The current version has strong psychometric properties and provides a very detailed assessment of communication development in all areas that are affected by autism. 20% of the assessments will be scored by two raters for reliability checks. This will be administered by a trained and experienced speech/language therapist. Two scores from this test will be used for primary analyses: Auditory Comprehension age equivalent score and Expressive Communication age equivalent score. The PLS is given at time points 3 & 4.

(2)MacArthur-Bates Communicative Development Inventory: Words and Gestures (CDI; Fenson et al., 1993) is a psychometrically strong parent questionnaire that evaluates words and gestures children use and understand in natural settings. Mitchell et al. (2006) recently reported that evaluation of words and gestures at 12 months on the CDI increased sensitivity for detecting children with ASD at 2 years. This will be used as a dependent measure of intervention efficacy.

(3) Mullen Scales of Early Learning (Mullen, 1995). As already described. The variables of interest are two ratio DQ scores, overall DQ and nonverbal DQ, described above. The ***Differential Abilities Scale*** (DAS; Elliot, 1990) described above, used if ceilings on Mullens occur.

(4) Vineland Adaptive Behavior Scales, Second edition (VABS II: (Sparrow, Balla, & Cicchetti, 2005). This consists of four domains of adaptive behavior: communication, self-care, social and motor skills. The fifth scale, maladaptive behaviors, will not be used because it is not normed for this age group. The VABS-II is a semi-standardized parent questionnaire or interview (it can be used either way) designed to assess children's behavior in real life, every day settings. It provides an assessment of functional skills in the domains of communication, daily living skills, socialization, and motor skills. The VABS-II has excellent psychometric properties and, for young children, requires 30 minutes or less to administer or complete. The VABS-II will be administered to the primary caretaker by telephone every six months and again at six months after the final in person assessment. The variables of interest are the age equivalent scores and the developmental quotients for two subscales: communication and social. The DQs will be calculated just as in the Mullen DQ scores are, in order to avoid problems with floor effects of standardized scores.

Autism symptoms:

(5) T-ADOS: The T-ADOS was described above. The ADOS will be used as a qualifying measure at enrollment, and as an outcome measure of symptom severity during the following years.

(6) Toddler ADI-R. This tool was described above. It will be used as a qualifying measure at enrollment and as an outcome measure 24 months after enrollment.

(7) PDDBI PDD Behavior Index – (Cohen, Schmidt-Lackner, Romanczyk, & Sudhalter, 2003) The PDD Behavior Inventory (PDDBI) is a rating scale filled out by teachers designed to assess response to intervention in children with PDD. Subscales measure both maladaptive and adaptive behaviors as well as a summary score that reflects overall severity. The scale has been shown to have very good internal consistency. Factor analyses have confirmed the structure of the scale. Comparisons with psychometrically sound instruments that assess autism severity, adaptive behavior, and maladaptive behavior reveal high correlations and document construct validity. Variables of interest: the subscale scores from the maladaptive and adaptive subscales as rated by the child's teacher. The PDDBI will be given only at time point 4.

Social domain:
(8) Peer relationships will be measured via two types of measures: teacher report and parent report.
Teacher report: **Vineland Adaptive Behavior Scale, second edition (VABSII): Teacher Rating Form** (Sparrow et al, 2005) Variable of interest: Social sub domain score. The VABSII- TRS will be given only at time point 4.
(9) Parent rating: Peer sub domain score from the Battelle Developmental Inventory 2nd edition (Newborg, Stock, Wnek, Guidubaldi, & Svinicki, 2005) The BDI is a valid, reliable, standardized assessment battery of key developmental skills in children from birth to eight years of age. The personal-social domain will be administered to the parent, which consists of multiple items that assess skills in a variety of sub domains, including adult interaction, expression of feelings/affect, self-concept, and peer interaction. Variable of interest: this sub domain score. BDI-PR-PS will be given at time points 2,3 and 4.
(10) Parent rating: VABS II: Social Domain: variable of interest, sub domain score. Rating taken at time points 1 and 2 and thereafter every 6 months and 6 months after the final in person assessment for *study completion.*

Measurement of independent variables affecting child outcomes. This is the final category of measures. We will examine variables involving (a) biological, (b) child specific, and (c) environmental factors that are expected to mediate or moderate child outcomes.

Biological variables: Physical and neurological exams will be completed once, during the initial evaluation, by a developmental pediatrician or a pediatrics fellow supervised by the developmental pediatrician, and reliability established for assessing dismorphic features and neurological abnormalities. Emphasis will be on major and minor congenital dismorphology indicative of alterations of early morphogenesis and genetic disorders. Wood's lamp examination of the skin will be completed to examine neurocutaneous lesions. Features indicative of syndromes known to be associated with autism and/or mental retardation (e.g., Fragile X syndrome, Tuberous Sclerosis) will be assessed and a standardized dismorphology exam will be conducted. Growth parameters will be assessed, including height, weight, and head circumference. A neurologic exam will be conducted to assess neurologic abnormalities, motor function, tone, and asymmetries. We will follow the procedures of Miles and Hillman (2000) to summarize the data. **Number of dysmorphic features, number of health related events, and number of abnormal neurological symptoms will be totaled and used as risk scores.** The medical exam and history is administered at time point 2.

If a FXS screen has not been completed and the child meets all other eligibility criteria, this will be provided by the study. All subjects who have not previously been karyotyped will have blood samples drawn at the respective sites Peripheral blood will be cultured and harvested using a standard high resolution banding technique (HRB). Chromosomes will be banded using the standard trypsin-giemsa staining technique (GTG). In each case the karyotype will be described using the International System for Human Cytogenetic Nomenclature (ISCN) nomenclature. Routine Fluorescence In Situ Hybridization (FISH) for 15q11.2 will performed on metaphase spreads for all the subjects. Twenty metaphase spreads will be analyzed by fluorescent microscopy using dual color filters for each subject.
Medical History A medical history including autoimmune, sleep and GI problems and evaluation will be completed on each subject. The AGRE (Autism Genetic Resource Exchange) Comprehensive Neurogenetic Evaluation will be used to standardize data collection of medical history and examination. Physical and neurological exams will be completed and documented by physicians experienced in evaluating children with autism and other neurodevelopmental disorders to evaluate for any syndromes known to be associated with autism and/or mental handicap, as well as to consistently document any dismorphology, or growth or neurological abnormalities according to AGRE evaluation format. Developmental and family history will be obtained through parental interview according to a standard questionnaire adapted from the Family History Interview and the M.I.N.D. Institute's Child Development Clinic Questionnaire.

Eye-Tracking Visual scanning and visual processing of a number of different sets of stimuli will be assessed using eye-tracking methodology. Eye-tracking will utilize the Tobii ET-17 binocular infrared bright-pupil corneal reflection video-oculographic eye-tracker that we have used in our lab previously. The Tobii system is particularly useful with infant and toddler age-groups because it does not require any head-mounted hardware and can reliably track visual point of regard without requiring anything more from the toddler than passive visual attention to the monitor. Data gathered during visual scanning of stimuli will be analyzed for preferential looking as an index of the ability to discriminate contrasting visual stimuli (e.g., motion direction, emotion

faces), the ability to integrate sensory information (e.g., speech and video; sound and animation), and attention control and processing speed. Eye-tracking will be used at all 4 assessment points in order to examine moderation of treatment response.

Child specific neuropsychological variables.

Rationale: The main dependent variables listed above will be gathered three times and represent summary variables of complex developmental skills or behaviors that have been found to predict outcomes in autism at the group level. We assume that more discrete, neuropsychological abilities underlie the development of these complex variables over time. In this study, we will test the role several discrete neuropsychological abilities in which there are known autism-specific impairments, as reviewed in the introduction. The neuropsychological abilities listed below represent the individual child characteristics in the model to be tested.

Imitation skills. Sixteen imitation tasks used in (Rogers, Hepburn, Stackhouse, & Wehner, 2003) will be administered, including: familiar and novel object imitations, manual and oral- facial gestural imitations. This scale has been used in several previous autism studies as well as current studies of toddler imitation ongoing in Dr. Rogers' laboratory. Each item will be live coded using one of three scores: full pass (2), partial pass (1), and failure (0) resulting in a total imitation score. This coding system is currently being used in Dr. Rogers's and Dr. Lord's labs, with excellent inter-rater reliability. The battery has demonstrated strong test-retest reliability (Rogers et al, 2003). The administration involves three rapid presentations of each behavior and rewards children for all attempts. Administration takes 15 – 20 minutes. The battery will be split in half and assessed on two different days, to prevent fatigue. The child's total score will be used as an overall score.

Social interest

Responsive Social (Joint) Orienting. The procedure consists of four social stimuli (voice, finger snap, clap, and hum) and four nonsocial stimuli (timer ticking, phone beep, sandpaper scratch, light switch click).All sounds will be delivered at the same decibel level and monitored through out. The procedure will be video recorded for reliability. Each sound will be delivered live, repeated three times each, with one second inter-stimulus interval, in counterbalanced order, in a quiet room at a time when the child is seated and engaged in a moderately interesting toy. Sounds will occur behind the child. Two raters observing the session via video will live code head turns towards the stimulus occurring within 10 seconds of the stimulus, and any discrepancies will be resolved via videotape. This procedure has been used in several experiments in the Dawson lab (Dawson et al., 2004), and the 2004 study reports an interclass correlation of 0.87 between live and video coding. Variables of interest involve number of head or eye turns to social and nonsocial stimuli.

Language and Play Variables:

Speech sample A speech sample will be gathered across the ADOS administration period and phonetically transcribed and analyzed to assess linguistic and phonological development. Method will include the procedures used by Carson, Klee, Carson, and Hime (2003), involving procedures for phonological assessment of two year olds. Productions will be phonetically transcribed, with appropriate inter-rater reliability. Key variables to be used in the analyses include (1) number of spontaneous episodes of initiating joint attention behavior, (2) number of different phonemes produced overall, and (3) different consonant cluster types in the initial and final position, which will provide an indicator of syllable shape complexity.

Language Use Inventory (O'Neill, 2002) – 20 minutes with parent. This parent-report questionnaire measures a broad range of pragmatic language skills typically exhibited by children 18 to 47 months of age. It is the only current effective measure of language pragmatics in preschool aged children. The LUI will be used at the last 2 assessment points to measure the pragmatic dimension of language, a prominent feature of language impairment in ASD.

Free Play Sample, Primary Caregiver (Rogers, S., Vismara, L., Goldring, S. 2007**)** This sample consists of a 10 minute videotaped play session with the primary caregiver (parent) and child. The play sample uses a set of toys, an unfamiliar environment, and a parent/primary caregiver. This procedure involves a play interaction between the child and primary caregiver (parent). It is employed to gather frequency data concerning use of verbal and nonverbal communicative behaviors. This procedure will be used in three ways: (1) to establish baseline rate of social communication before treatment begins, (2) to sample generalization of social communication during the treatment period, and (3) to sample maintenance of social communication during follow-up points after treatment ends.

Free Play Sample, Alternate Primary Caregiver (Rogers, S., Vismara, L., Goldring, S. 2007) This sample consists of a 10 minute videotaped play session with the alternate primary caregiver and child. The play

sample uses a set of toys, an unfamiliar environment, and an alternate primary caregiver in order to promote playful interaction between the child and an alternate caregiver. It is employed to measure whether the treatment techniques used by the primary caregiver are also demonstrated by the alternate caregiver over time. Frequency data concerning use of verbal and nonverbal communicative behaviors is collected. This procedure will be used in three additional ways: (1) to establish baseline rate of social communication before treatment begins, (2) to sample generalization of social communication during the treatment period, and (3) to sample maintenance of social communication during follow-up points until treatment ends.

(2) Play variables to be used in the analyses include frequency of functional and symbolic play acts, and number of novel functional and symbolic play acts, coded from the free play samples described above.

Medial Temporal Lobe measures. The **Object discrimination reversal task** has been demonstrated to dissociate ventromedial prefrontal cortex impairment from dorsolateral prefrontal cortex impairment in animal studies (Dias, Robbins, & Roberts, 1996). Performance on this task is severely impaired by both early and late lesions to the orbitofrontal region in animals and lesions of the ventromedial prefrontal region in human adults (Damasio, 1994). As used by (Dawson et al., 2002), subjects are first taught which of two objects will yield a reward. After the subject has learned this rule and reached for the target 5 times consecutively, a reversal occurs and now the reward is linked to the other object. Trials continue through 25 or until two reversals occur. Dependent variables include: percentage of times the child meets criteria for a correct performance, total number of errors, and total number of preservative errors (errors following an error). Trials will be coded by the examiner and reliability checked via videotape. The ODR will be used at timepoints 2, 3 & 4.

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Social environmental variables. *Methodology for determining risk/protective factors.* Following Dunst's (1993) literature review and model of risks and opportunities, we will gather information on biological risks through the ACE physical/neurologic exam and history and the social risk/opportunity variables described below. Each variable will be gathered only at the initial visit, unless stated differently in the item description. Each child will have a risk and opportunity rating for each biological risk and each social risk. These will be totaled and the total number of risks and opportunities will be the variables used in analyses.

For each variable, we will follow the procedures described in Barocas, Seifer, & Sameroff (1985) for categorizing each variable as a risk or opportunity for a particular child. For items considered definite risk by Barocas et al, 1985 (e.g. single parent, presence of diagnosed mental illness in mother), we will use the same criteria to determine risk. For other items, Barocas et al (1985) used the group mean to determine risk. Since none of the measures have norms for families of children with autism, we will follow the Barocas et al 1985 practice: using the group mean as the cutoff for risk, with a score below the group mean considered a risk, and that above the group mean considered an opportunity or protective feature. Using the subject group of 108 as the basis for establishing risk status appears justified given that the goal is to model the relations between socio-cultural variables and outcomes for this particular group of subjects. Basing the determination of risk on the sample data rather than national or measure norms assures that the assignment of risk and opportunity reflects both the sociometrics of the children's regions and the unique impact of having a toddler with diagnosed autism.

General family demographics The general demographic questionnaire contains questions concerning family composition, family size, number of people in the house, parents' educational levels, parents' occupations, and annual gross incomes. These five questions will each be scored as a risk or opportunity. Single parenting and unmarried parenting will be considered a risk; two parent married families an opportunity. Each of the other four questions will be rated as a risk or opportunity based on the group means.

Questionnaire on Resources and Stress (Konstantareas et al., 1992) will be administered to both parents at all 4 time points. It assesses factors such as time demands, attitudes, social support, pessimism, family integration, and financial problems. It has been validated with families of children with autism, mental retardation, learning-disabilities, and asymptomatic children, showing good internal consistency, split-half reliability, and stability.

Life Experiences Survey (Sarason et al., 1978) will be administered to will be administered to both parents at all 4 assessment time points. It is a 57-item self-report measure, which asks respondents to indicate significant events they have experienced during a preceding time period and to rate whether the event was positive or negative and the extent to which the event has affected his or her life.

Dyadic Adjustment Scale (Spanier, 1976) will be administered to mothers and fathers at all 4 assessment time points. It assesses quality of the respondent's marriage or relationship and has good content, criterion-related, and construct validity.

Social Support Questionnaire (Sarason et al., 1983) will be administered to both parents at all 4 assessment time points. -It assesses perceived support from family and friends.

Parenting Sense of Competence Scale (PSCS) will be administered to mothers and fathers at all 4 assessment time points to assess feelings of parental efficacy and parenting satisfaction. Acceptable reliability and validity have been reported (Johnson & Marsh, 1989).

Parental mental health.

Symptom Checklist-90-Revised SCL90R (Derogatis, 1994)

We will administer the Symptom Checklist-90-Revised SCL90R (Derogatis, 1994), a measure of current, point-in-time, psychological symptom status comprised of 90 items it requires 12-15 minutes. There are three global indices of distress, the Global Severity Index (GSI0), the Positive Symptom Distress Index (PSDI), and the Positive Symptom Total (PST). The GSI is the best single summary measure and will be used to detect clinical levels of psychopathology. Variables to be used in the analyses involve risk or opportunity rating. Risk status will be assigned if a parent meets the clinical cutoff of the GSI. Opportunity status will be assigned based on reported absence of mental health concerns. This will be gathered from both parents at the first and final visits, time points 1 and 4.

Data reduction. The number of risks/opportunities form the above measures will be totaled into one variable; this will be the variable of interest used in the analyses.

Maternal-child interaction styles. The next two variables involve measures of mother-child interaction. Since these constructs have already been found to influence child outcomes, these two variables will be coded in a continuous coding approach, described below.

Samples of mother-child play will be gathered during the latter part of the lab visit. The parent will be asked to play with their children for 15 minutes in a standard room free of all other objects or distractions. During the first three minutes, three developmentally appropriate toys will be available for a warm-up. After this, videotaping will begin, and the experimenter will bring in two puzzles and a snack. The mother will be asked to spend five minutes playing with each puzzle with her child. The first puzzle will be easy relative to the child's MA and the second puzzle will be challenging. After 10 minutes with the puzzles, the dyad will be asked to clean up for two minutes. After cleanup the mother will be asked to play a game without objects with her child for 2 minutes. The remaining 5 minutes will involve the dyad enjoying a snack together. Scores will be obtained for the entire 15 minute period. This procedure will be repeated annually for a longitudinal analysis.

Trained and reliable observers blind to groups and hypotheses will code the videotapes with the Maternal Behavior Rating Scale (MBRS; (Kim & Mahoney, 2004). The MBRS consists of 12 global items, each of which reflects features of interactive style that have been reported to relate to children's rate of cognitive, language, or social development. Items are rated on a 5 point Likert scale. Scores of the 12 items are tallied to four subscales: Responsivity (responsiveness, sensitivity, effectiveness), Affect (acceptance, enjoyment, expressiveness, warmth), Achievement orientation (praise, achievement), and Directiveness (directiveness, pace). The variable used in the analyses will be a summary score of these four subscores. This will be gathered at each annual visit.

Maternal-child number of learning opportunities. A second coding system will be used on these tapes. Following recommendations made by Wolery & Garfinkle (2002), the videos will be coded by trained and reliable coders for number of child learning opportunities. A "successful learning opportunity" is defined as a maternal-child interaction in which there is an antecedent act (A) initiated by mother, a responsive child behavior (B), and a contingent response (C) from the parent that delivers feedback to the child about the adequacy of the child's behavior. Each A-B-C occurrence will be counted as one learning opportunity. Occurrences in which incorrect or inappropriate behavior is reinforced, occurrences in which a child is scolded or told no without a correction or model for support for correct response, and occurrences in which correct or desired behavior is ignored, will be counted as "failed learning opportunities". Two scores will result, (1) the number of successful child learning opportunities per 10 minutes of play, and (2) the ratio of successful learning opportunities to failed learning opportunities. This will be multiplied to provide a summary score. This will be gathered at each annual visit.

The NCAST (Nursing Child Assessment Satellite Training) measures of parent-child interaction were developed by Kathryn Barnard at the University of Washington. For this study, the teaching scale only will be used. During a teaching episode, the provider will ask the mother to choose an activity that her infant cannot do from a list of Birth-to-Three developmental tasks (e.g., imitate the mother's actions). The mother will be

asked to help the infant achieve this task. The NCAST Teaching Scale (Barnard, 1989; 1994) will be used to code the mother-infant videotaped interaction. The Teaching Scale is organized into six subscales: parent sensitivity to cues, parent response to infant's distress, parent social-emotional growth fostering, parent cognitive growth fostering, infant clarity of cues, and infant responsiveness and initiations with caregiver. A contingency subscale measures the amount and quality of parental contingent behavior towards the infant. The scale consists of 73 binary items that produce two summary scores, one score for the parent's interaction with the infant, and one score for the infant's interaction with the parent. In addition, subscale scores can be calculated for each of the six subscales described above. The NCAST Teaching Scale has been demonstrated to be sensitive to changes in caregiver-infant interaction in response to early parent-training interventions (Kelly et al., submitted) and is a valid predictor of child IQ and language outcomes at 3-5 years of age, and of first grade school behavior as rated by teachers (Kelly & Barnard, 2000)

Intervention history: **CPEA Network Early Intervention Interview** (Dawson, Sigman, & Rogers, 2003). This interview requires 20 minutes or less and systematically assesses the child's current and past intervention history, accounting for all types and amounts of intervention experienced and providing a formula for calculating total number of hours of various kinds of intervention. This tool provides a method for deriving a single summary score that represents the number of hours of 1:1 intervention experienced, calculated for each intervention experience by number of hours of intervention divided by adult: child ratio. This will be gathered every six months by telephone.

Social-environmental variable reduction: Four scores will be used in the analyses from these measures: number of social-environmental risks/opportunities, maternal style score, (mean number of learning opportunities with the parent in 10 minutes) times (ratio of successful to failed attempts), and the summary number of 1:1 equivalent hours of intervention received.

Social validation of the intervention. The final area of assessment involves the social validity of the intervention approaches being examined in this study. Two social validation measures will be used.

(1) The Parent Satisfaction Rating (Charlop-Christy & Carpenter, 2000) will be administered to the parents in the two groups at time points 2, 3 & 4. This tool allows parents to rate the ease of implementation in the home and their opinions concerning intervention utility. Parent scores will be calculated for the experimental intervention and compared to scores of the comparison group to examine parent ratings of ease and acceptability of the experimental intervention.

(2) The Working Alliance Scale for Interventions with Children (Davis, Kuhn, & Carter, 2006). This measure was created as an adaptation of an existing working alliance scale. A pilot study exploring scale internal reliability and scale properties was conducted in the winter of 2004 and results were presented at an annual conference on research in autism .These initial analyses found strong internal consistency among scale items (alpha = 0.91) and variability in the range of reported scores. These measures will be used to describe the response of the families to the experimental intervention at time points 2, 3 & 4.

6. If blood samples will be collected, identify in what manner:
   XX___venipuncture ___venous catheter ___arterial puncture ___arterial catheter ___cutaneous

7. Any additional procedures (noninvasive) involved in this study activity must be described.
   N/A
8. If the study involves incomplete disclosure, provide the rationale.

9. If this activity will be utilizing existing data, specify the source and how the data will be retrieved, reviewed, coded and stored.
   N/A
10. Address the location and duration of the study.
    This study will be conducted at the MIND Institute and in family homes and other child care settings and will last for five years.

11. Clarify how you plan to monitor data to ensure subject safety (i.e., labs monitored for abnormalities, questionnaires monitored for suicidality).
    There will be an external data and safety monitoring board. Children will be monitored daily by project personnel and also by parents. All adverse effects will be reported to the PI, the Data safety and Monitoring Board, and the IRB by the PI.

12. Address whether you have the appropriate resources (study personnel and facilities) to conduct this study.
    We have the needed facilities to conduct this study. We have the needed personnel.

13. Describe the role of each key member of your study personnel.

Administrative team

Sally J. Rogers, Ph.D. (Project Director, 20%effort, 2.4 calendar months)
Expertise: Dr. Rogers is the originator of the Denver Model and has been developing, refining, teaching, delivering, and studying this model on young children with autism for the past 25 years. She directed a large treatment center using the model for 15 years in Denver. She also has considerable experience in directing large research projects involving early autism studies, including being PI of one of the CPEA centers for the past 10 years, and partnering with Dr. Dawson to conduct the large clinical trial of the Early Start Denver Model at University of Washington.

Role: PI. Dr. Rogers will be responsible for the overall direction and administration of this research network. She will work directly with the PI's of the other two sites and the DCC to assure that all aspects of the study are proceeding as planned, and to address any potential problems as they arise. She will be responsible for the fidelity of the intervention delivery across all sites, both training supervisors and therapists initially and maintaining fidelity to the model throughout the study. In the Sacramento site, she will supervise all aspects of the project, and directly supervise the leader of the evaluation team and of the intervention team. She will be responsible for managing the grant budget and completing all progress reports and paperwork related to the grant, and she will coordinate efforts with the DCC PI and the Data and Safety Monitoring Board.

Kacy McKinley, Clinical Research Coordinator (10%)
Ms. McKinley will assist Dr. Rogers in administering all aspects of this project, including arranging monthly conference calls, setting up all onsite and cross site training, arranging grant related travel, preparing NIH reports, manuscripts, purchasing, tracking budgets, managing travel reimbursements and other reimbursements for subjects and staff, assisting Dr. Rogers with the IRB communications, and managing all communications.

Gregory S. Young, Ph.D. (Fidelity and Reliability Coordinator, 5% effort)
Dr. Young is a developmental psychologist with expertise in several different areas, including database design and management, statistical analysis, and use of technology. He has considerable experience managing large groups of lab personnel from his previous position as lab manager for Dr. Ozonoff and Dr. Rogers lab at the MIND Institute, where he has managed a group of over 30 research assistants and staff members. Dr. Young will have two main responsibilities on this project. First is quality control. He will be responsible for assuring that all sites are carrying out the evaluation and the intervention components of this project with uniform high quality procedures. To that end, he will work with the PI's to establish uniform standards for administering and scoring all measures and for conducting all aspects of the intervention. Then, he will be responsible for designing and conducting training and monitoring activities for key staff at all sites so assure that relevant staff learn the standards and adhere to them throughout the years of the project. Thus, he will design and conduct training activities, procedures manuals, training videos, and fidelity assurance procedures for all aspects of the project. He will work with each site to design reliability tracking systems and coding teams and he will coordinate with the Data Coordinating Center for this project at University of Washington to assure timely gathering of reliability and fidelity data and for monitoring the quantitative aspects of reliability and fidelity. His second main responsibility will involve database design and management, data cleaning and data transfer for the Sacramento site. He will coordinate with Dr. Jeff Munson in Seattle and with Dr. Fitzpatrick, head of the DCC, to assure accurate and timely data entry and data transfer to the DCC. He will work with Dr. Rogers to prepare reports as needed, for NIH reports, IRB reports, and scientific papers. He will also work with Dr. Munson and Dr. Fitzpatrick on statistical analysis for this project. Finally, he will train and supervise research assistants working as volunteers on this project in the Sacramento site.

Jennifer Bernstein (30%) Jennifer Bernstein will assist Dr. Young with responsibilities involving gathering, coding, and analyzing data and managing data bases. Additionally, she will maintain the lab website. Finally, she will train and schedule student workers to record video sessions, and she will also record sessions as needed.

Recruitment and Evaluation Team:Beth Goodlin-Jones, Ph.D. (Assessment Team Coordinator, 20%)

Dr. Goodlin-Jones is a developmental psychologist with considerable experience in early autism. She is currently the co-PI of the MIND Institute Subject Recruitment and Qualification Core. She will be responsible for coordinating recruitment and evaluation of all the subjects for this study. She will supervise the rest of the evaluation team, will work with Dr. Rogers assistant to schedule evaluations, will conduct the annual assessments when needed, will work with Dr. Fitzpatrick of the DCC to randomize children into groups, and work with Dr. Young regarding data entry and data quality of administration and scoring procedures and data cleaning and entry. She will work directly under Dr. Rogers in this project. Dr. Goodlin-Jones will also head the Evaluation team and train and supervise all who work in evaluation activities on this project. She will also be involved in recruitment of new families to the study.

Carolyn McCormick, Graduate Student (50%):
Carolyn McCormick is a graduate student in psychology. Her primary responsibilities are administering, scoring and writing reports for the yearly evaluations under the supervision of Dr. Beth Goodlin-Jones. She also supports Dr. Gregory Young in data coordination and statistical analyses for the project.

Maria Fusaro, Ed.D. Post-Doctoral Fellow (10%)
Maria Fusaro's primary responsibilities are administering assessments under the supervision of Dr. Beth Goodlin-Jones, and consenting families when needed. She also supports the project by conducting secondary data analysis on children's use of gestures.

Postdoctoral fellows and graduate students: two graduate or postgraduate trainees from psychology or human development will be assigned to this project to assist in evaluating participants. The student will be trained and supervised by Dr. Goodlin-Jones, who is a faculty member of the graduate groups of both Psychology and Human Development departments. The trainees will be trained to administer and code all the instruments in the assessment battery.

Robin Hansen, M.D. (Developmental Pediatrician 5%)
Dr. Hansen is the Director of Clinical Programs at the UC Davis M.I.N.D. Institute and Professor and Chief of Developmental-Behavioral Pediatrics, Department of Pediatrics, School of Medicine. Dr. Hansen is a developmental-behavioral pediatrician/researcher with vast experience in treating children with neurodevelopmental problems such as pervasive developmental disorder, autism, learning disorders, and attention deficits. She heads a multidisciplinary clinic that diagnosis children, plans/initiates intervention strategies, and works closely with patient families. In this clinic Dr. Hansen trains and supervises the physicians who rotate through the clinic as a part of their fellowship program. Dr. Hansen's role on the project will to conduct and to supervise fellows who conduct the physical and neurological examinations of all of the children enrolled in the project.

Intervention Team:
Janice Enriquez, Ph.D., (Clinical Intervention Support 5%)
Janice Enriquez, Ph.D. is a developmental and licensed clinical psychologist. She will provide clinical support to the Intervention team regarding all subjects. She will meet weekly with the Treatment Team manager and Treatment Team Leads to discuss any clinical issues and provide recommendations when needed.

Aimee Bord, CCC-SLP Speech/language pathologist (10%)
Aimee Bord, CCC-SLP is an experienced speech pathologist has considerable background in both assessment and intervention of young children with autism. Her responsibilities will involve assuring that each child in the experimental group is receiving very high quality language intervention in the project. She will see assess each child quarterly during the child's biweekly clinic visit, will examine each child's intervention objectives and assure that the communication objectives are appropriate, and will review the teaching plans for each child and observe the child's intervention during their clinic visit biweekly, to assure that the communicative and language aspects of their intervention is being carried out appropriately. She will train the community health workers in carrying out the communication objectives on a daily basis when additional training is needed. She will assist the team in determining when children are in need of additional speech/language services and will assist with referrals as needed. Thus, she will provide professional clinical oversight and supervision of the communication arm of this intervention.
Occupational therapist, to be hired in year 3 (5%)

The responsibilities will involve assuring that the sensory motor and adaptive needs each child in the experimental group. She will assess each child quarterly during the child's biweekly clinic visit, will examine each child's intervention objectives and assure that the motor and adaptive objectives are appropriate, and will review the teaching plans for each child and observe the child's intervention during a clinic visit monthly, to assure that the motor and sensory aspects of their intervention is being carried out appropriately. She will train the community health workers in carrying out the motor objectives on a daily basis when additional training is needed. She will assist the team in determining when children are in need of additional OT or PT services and will assist with referrals as needed.

Laurie Vismara, Ph.D. (Training Coordinator, 10%)
Dr. Vismara is a behavioral and educational psychologist with expertise in Pivotal Response Training from her graduate training with Lynn and Robert Koegel at Univ. Cal Santa Barbara. She also has expertise in the Early Start Denver Model from her postdoctoral training with Dr. Rogers. She has specific expertise in parent training and contributed to the parent training curriculum to be used in this project. She is currently completing her BCBA, Board Certified Behavior Analyst. Her roles include training, intervention fidelity management, and intervention supervisor. Dr. Vismara will initially organize and carry out the training plan for the intervention supervisors and therapy assistants across the sites as well as participate in the active training in this site. As intervention fidelity manager she will supervise and organize the intervention fidelity data collection on all therapy assistants across all three sites. As a team leader with the other two team leaders, she will be plan, organize, direct, and oversee the intervention of seven subjects in the experimental group. She will carry out the curriculum assessment, write the 12 week intervention objectives, develop the daily intervention plan, and train the community health workers to carry out the intervention daily in the child's home. She will assess the daily progress data collected for each child and update the daily program accordingly to assure the child's most rapid progress. She will monitor the quality of teaching carried out by the interventionists during their work with children on the Clinical Competency Checklist and train as needed. Additionally, she will provide the 12 week training program to the parents of each of these children, as described in the Early Start Denver Model Parent Manual, and she will monitor parent interventions to assure maintenance and generalization of parent skills.

Marie Rocha Ph.D. (Treatment Team Manager): Dr. Rocha is a developmental behaviorist with early intervention experience with young children. Her position will have the same responsibilities in terms of leading intervention teams as Dr. Vismara, described just above. She is experienced in delivering a range of empirically supported interventions for young children with autism, and also experienced in supervising others in intervention delivery. She has a Doctoral Degree in Psychology with an emphasis in Applied Behavioral Analysis (ABA).

Vanessa M. Avila-Pons, M.A. (Treatment Team Leader): Ms. Avila-Pons is experienced in working with children with autism and their families, which has included developing and managing home and school based intervention programs for children in community based treatment programs, using empirically supported interventions. As a team leader, her primary responsibilities are to plan, organize, direct and oversee the intervention of up to 7 subjects in the experimental group. She will carry out the curriculum assessment, write the 12 week intervention objectives, develop the daily intervention plan, and assist the treatment manager with the training of the community health workers to carry out daily intervention.
Interventionists (Community Health Workers) (4 - 6 fulltime).
These positions are responsible for delivering the experimental intervention in the children's homes. The positions are supervised by the clinical psychologist, and trained and overseen by the team leader. The people in these positions will have college degrees in psychology, education, communication, or some related field, and will have previous experience delivering individual intervention to young children with autism, with strong letters of recommendation from employers. They will all receive in depth training in this project before they begin to work with children, and will be carefully supervised throughout their work on the project. They will deliver 15 intervention sessions per week, will meet weekly for group supervision, and will have monthly in-service trainings to continue to develop their skills.

Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) is designed to assure the safety and wellbeing of the subjects and their families and the validity of the data. The DSMB for this study was established by the NIH and consists of a number of experts in child safety and wellbeing, research design and ethics. The members are Maria Brooks, Ph.D. University of Pittsburgh, Tristram Smith Ph.D. University of Rochester, Stephen Warren Ph.D. University of Kansas, Marsha Seltzer, University of Wisconsin, and Andrew Benjamin, University of Washington. This DSMB receives quarterly reports from the Study, developed by all three sites, regarding recruitment, screening, enrollment, attrition, compliance, and adverse events. Dr. Rogers will communicate monthly with the DSMB interface for this study (Dr. A. Fitzpatrick of the University of Washington) regarding all aspects of the study.

SUBJECT SELECTION:

1. Identify the subject population. See below
2. Address how subjects will be recruited: _XX__direct person to person solicitation, __XX_by telephone, _XX__letter, ___advertisement, ___press release, _XX_notices, ___other. Flyer and brochure attached.
3. State from where subjects will be recruited, when and how many. See below
4. Specify the age of the research subjects. See below
5. List all criteria for including and excluding subjects. See below
6. If women and minorities are excluded, provide rationale for such exclusion. N/A

Participants

108 toddlers with Autistic Disorder will be recruited from three sites: 36 from Sacramento, California and the surrounding region (a population base of over 2 million), 36 from greater Seattle region in Washington State (a population base of over 3.5 million), and 36 from Ann Arbor, Michigan and the surrounding area including Detroit (a population base of over 5 million). Both males and females will be recruited, from all ethnic groups and socioeconomic backgrounds. Participants are expected to represent the minority distributions of their respective communities, as described below. Recruitment procedures will be carried out in each of the community settings to disseminate information about the study to members of various ethnic groups, and targeted recruitment efforts will be made to recruit minority families. The power analysis supporting the total number of children is provided in the data analysis section below.

D.2.a. Inclusion criteria for children enrolled in the study are:

1. 12-24 months of age;
2. Must meet strict diagnostic criteria for idiopathic Autistic Disorder (a. diagnosis of autism by clinicians in a major autism diagnostic facility; b. clinical consensus of diagnosis of autism by two project psychologists, c. meets full autism criteria on the Toddler Autism Diagnostic Interview-Revised (TADI-R; Lord et al, 1995), and d. meets autism cutoff on the Toddler Autism Diagnostic Observation Schedule (T-ADOS);
3. Exhibit an overall developmental quotient is 35 or higher on Mullen Scales of Early Learning (Mullen, 1995);
4. Agreement to participate in a 12 week clinic based parent coaching phase and attend at least 75% of the sessions.
5. Agreement to have therapy assistants in the home 20 hours per week and attend a clinic team meeting twice each month;
6. Agreement to carry out the home program for 45-60 minutes daily, and to keep the required written data from the home program over the 28 months of enrollment in the project;
7. English as one language spoken to the child at home (because our therapists have not been trained to deliver the interventions in another language);
8. Attendance at all evaluation sessions, and no failure to keep appointments without calling to cancel during the intake period;
9. Hearing and vision screen within the normal range.

10. Independent ambulation by crawling or walking and no significant motor impairments (e.g.cerebral palsy, hemiplegia)

D.2.b. Exclusion criteria include:

1. Any other identifiable genetic condition associated with autism or with mental retardation (e.g. fragile X syndrome, Down syndrome), head trauma, known neurological disease (e.g., encephalitis), epilepsy with anti-convulsant medication, or significant sensory or motor impairment (e.g., cerebral palsy). An abnormal EEG alone or a history of an occasional febrile seizure, without an accompanying diagnosis of epilepsy, will not exclude a child from the study.
2. Birth weight <1600 grams and/or gestational age < 34 wks, history of intraventricular hemorrhage, exposure to neurotoxins (including alcohol, drugs);
3. Serious parental substance abuse, bipolar disorder, or psychosis in the primary care providing parent is another exclusion factor.
4. Living distance more than one-half hour from M.I.N.D. Institute.

D.2.c. Enrollment in other interventions.

All families will be referred to the appropriate community service programs, if they have not been referred previously. There will be no limitations on families who choose to enroll their child in any intervention (e.g., occupational or speech therapy, developmental preschool) at any time during the study, except for intervention in intensive behavioral intervention for more than 5 hours per week. At the time of enrollment and quarterly throughout the 28 months after enrollment, a detailed history will be taken of all the child's intervention experiences.

D.3.e. Randomization Procedures. Randomization will be carried out by the DCC using a stratified block design. At each site, toddlers evaluated for inclusion in the study will be classified by gender and severity of cognitive impairment using Mullen DQ (based on mean full-scale ratio DQ of the four main subscales of the Mullen Scales of Early Learning of <55 and >= 55). Using a computer generated random number, assignment to intervention group will be made by the DCC when eligibility of participants is ascertained and cell classification (by gender and severity) will be noted. The next child meeting qualifications for that cell will be placed in the alternate intervention. Using this schema will result in a balanced design by intervention (18 per intervention group for a total of 36 participants per site) and gender/severity (4-5 per group within each intervention) at end of recruitment.

Once a participant is randomized into experimental or community intervention, the DCC will communicate the assignment to the clinical psychologist on the Intervention Team, who will communicate this information to the families. Thus, the Evaluation Team is kept blind to group assignment. For children assigned to the experimental intervention, the psychologist will notify the Treatment Team coordinator to assign a team leader and schedule the first clinic visit for the curriculum assessment, and parent-toddler intervention will begin. Providing that more than 75% of the parent coaching sessions have been kept and the child continues to qualify for the study (I.e., meet inclusion criteria stated above) the family and child will continue on to the in-home intensive phase.

D.3.f. Community intervention group. For families randomized to community intervention, the project will continue to provide help and support until other professionals begin intervention and care can be transferred. This will be done in three ways. First, the professional reports that the diagnostic team writes will be provided directly to the parent and will assist in the referral process, by having a no-cost diagnostic assessment with recommendations for intervention. Second, the clinical psychologist who met with the family and informed them about the randomization outcome will continue to make monthly phone calls to the family for three months, unless the family declines these calls, to monitor their progress and assist them in gaining services for their child through the community system.

Third, the professional members of the intervention team will provide a kit created by the organization Autism Speaks called the 100 Day Kit that includes topics such as: (1) What is autism? (2) various treatment approaches (3)medical issues involved with autism (4) family issues that arise. The staff member who conducts the monitoring calls will answer parent questions. Thus, across these three activities, the project will provide considerable support for the community service group, as well as the experimental group.

SPECIAL/VULNERABLE POPULATON (if applicable)*:*

Surrogate consent for participation in a research study should be employed only to the extent that it is consistent with the intent of the Common Rule (45 CFR 46, Subpart A) and all other federal and state laws and regulations pertaining to protecting human subjects participating in research. Carefully review the IRB Policy on *Surrogate Consent For Research*

for compliance with all applicable laws, regulations, and conditions of this policy. Investigators are reminded that use of surrogate consent shall apply on a case-by-case basis within the protocol.

1. Identify the vulnerable population: _xx__children, _xx__mentally handicapped, ___pregnant women, ___fetuses, ___prisoners, _xx__cognitive impairment, ___life-threatening disease, or ___social or ___economically disadvantaged. Address what additional safeguards you will put into place to protect the rights and welfare of this population. Very low risk procedures, direct monitoring by parents and experimenters to assure welfare of subjects.

At the beginning of the first visit, the first phase of a two part consent process will be carried out. The initial consent form for the eligibility assessment phase of this project will be verbally reviewed with the parent by a senior project researcher. Those obtaining informed consent will have been trained and credentialed by the UC Davis IRB procedures. Parents' questions will be elicited and answered before proceeding further. Given the very young ages of these children, formal child assent will not be gathered. However, the child's behavior during assessment procedures will be considered to reflect their assent. Children who clearly protest participating in the study procedures will be considered as not consenting to the procedures and will not be coerced in to complying.

Families will also receive information that a certificate of confidentiality is in process with the NIH and will be presented to them once approval is given from NIMH. A certificate of confidentiality has been applied for with the National Institutes of Mental Health (NIMH) which is part of the U.S. Department of Health and Human Services (DHHS), an agency of the U.S. Government. With this document obtained, we (the investigators) cannot be forced (e.g. by court subpoena) to disclose information that may identify any family member in any federal, state, or local civil or criminal, administrative, legislative, or other proceedings. A judge may ask to look at these documents to decide whether or not the information can be used. All families will be aware that the disclosure of their or their child's identity may be found necessary upon the request of DHHS for the purposes of audit or evaluation.

After the consent from is fully discussed and signed the assessment will begin in the assessment room. Once the assessments are completed, there will be a break of approximately 15 minutes during which time the measures will be scored to determine if the participating child meets study criteria.

If a child meets study criteria and is deemed eligible, the family will be fully informed and fully consented for participation in the intervention phase of the study. The same procedure will be used as described above for the eligibility assessment consent.

A third consent form for monitoring visits is also part of this study. A monitoring visit is completed when a family asks to participate but their child is under 12 months of age or when the child is between 12-24 months of age yet there is no opening in the study schedule. The monitoring visit is a brief 45 minute visit with parent and child and the clinician meets and interacts with them in a comfortable setting. No formal assessment is conducted. The parent's concerns are reviewed and a mutually agreed upon return visit for an assessment is planned, if appropriate.

2. If you are seeking IRB approval for use of surrogate consent, justify the appropriateness of such use and describe your specific plan for the assessment of the decision-making capacity of the subject(s). N/A

RISKS:

1. Address whether there is a possibility of physical, psychological, social or legal injury from participation in this study and assess the likelihood and seriousness of those risks.

This study involves minimal risks. If children become distressed the procedures will be stopped. We do not think this distress is enough to cause physical or psychological injury.

2. If the methods of research create potential risks, describe other methods, if any, that were considered and why they will not be used.

NA

3. Identify your plan for protecting subject privacy and confidentiality.

Risks to confidentiality will be managed by using ID numbers rather than names on files, limiting access to the data to trained project staff, keeping all data and tapes in locked computer or standing files, and in locked rooms, having all staff trained in research ethics, and giving parents control over the uses of the videotapes and data beyond this study.

4. Explain your plan for reporting adverse and serious adverse events to the IRB.

Parents or parentally assigned caretakers will be present at all times in both the visits to the clinic and during the intensive treatment visits carried out in the home. Lab and home environments used for assessment or intervention will be "child-proofed" to make it very safe for infants and toddlers. If children become distressed, procedures will be stopped. Children will be given breaks and snacks and care as needed. The project personnel will be clinically skilled people with experience working with young children with disabilities. Scheduling will be done to fit into the family routines as much as possible. Furthermore, parents will receive the project coordinator and the principal investigator's telephone number and they will be encouraged to contact us in case they think adverse events occurred during and/or as a consequence of the experimental procedure. Adverse events will be reported to the IRB by using the sample Table for Reporting Serious Adverse Events/Injuries on the Human Research Protection web site. An external Data and Safety Monitoring Board has been formed by NIMH and Dr. Rogers and Dr. Fitzpatrick (University of Washington). All adverse events will be reported to this group as well as the IRB immediately after they occur.

5. If the study involves the use of placebo, justify why this is appropriate.

NA

BENEFITS*:*

1. Address if there is a benefit to individual subjects or to the particular group or class.

One benefit to individual participants is the feedback that will be provided to parents about their child's performance on all standardized developmental tests. A second benefit is the material provided to all families, community referrals to treatment provided to all families, and the follow up phone calls or personal contacts provided to all families as they move into intervention activities. Further, the intervention participants will receive an empirically supported developmental intervention shown to improve the core symptoms of autism and the developmental trajectories of children with autism.

2. Address if there is no direct benefit to the subject.

NA

RISK-BENEFIT RATIO:

1. Address whether the risks to subjects are reasonable in relation to the benefits.

Since the risks involved in these studies are minimal, we believe that they are outweighed by the benefits. The results of this project will be quite helpful in providing a deeper understanding of the nature of some key early developmental processes in autism. Children in the intervention group will receive a very high quality and intensive intervention at no cost for two years and are likely to benefit from this intervention. All children, in both groups, will receive referrals, yearly evaluations, and clinical reports and guidance. All parents will receive training in maximizing their child's skills and minimizing behavioral problems.

COSTS/COMPENSATION TO SUBJECTS:

1. If the study involves the possibility of added expenses to the subject or to a third party, such as an insurer (e.g.,

longer hospitalization, extra laboratory tests, travel) address the magnitude of those expenses and how this is justified.

There are no direct costs to participants, other than that associated with travel. A small amount of money (gift card for $50) will be offered to each family at the end of the fourth visit (Visit 4 A/B) for both groups to encourage completion of all paperwork and interviews in a timely manner. Subjects will not be asked for their social security number in order to receive the gift card.

2. Describe the amount and type of compensation that will be paid to subjects and how that compensation will be staged/pro-rated.

Subjects will not receive monetary compensation for costs associated with clinic visits. They will receive interventions at no personal cost. All families will be provided with a $50 gift card at the end of visit 4A/B when all paperwork and questionnaires are completed to assist in successful completion of the study for both community control and intervention groups.

DISCLOSURE OF PERSONAL AND FINANCIAL INTEREST:

1. Disclose any personal and financial interest in the research as well as the extent of personal and financial interest in the sponsor.

There is no conflict of interest involving this project. None of the research staff have any personal or financial interest in the studies or sponsor.

INVESTIGATIONAL DRUG (if applicable): NA

INVESTIGATIONAL DEVICE (if applicable): NA

WAIVER OF INFORMED CONSENT (if applicable): NA

TOTAL NUMBER OF COPIES REQUIRED FOR SUBMISSION TO THE IRB Administration:

Clinical: Original plus 24 copies
Social & Behavioral: Original plus 18 copies

IRB Administration
CRISP Bldg., Suite 1400, Room 1429, UCDMC

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