Protocol Number:	Q170886
Protocol Title:	Cognoa ASD Diagnosis Aid Validation Study
NCT Number:	NCT04151290
Protocol Date:	Version 3.0, Dated February 3, 2020

TITLE PAGE

Protocol Number:	Q170886
Protocol Title:	Cognoa ASD Diagnosis Aid Validation Study
Sponsor:	Cognoa, Inc. 2185 Park Blvd. Palo Alto, CA 94306 Telephone: (408) 207-6659 Contact: Minda Seal Email: minda.seal@cognoa.com
Version, Date:	Version 3.0, Dated February 3, 2020

Statement of Compliance
The study will be conducted in accordance with the design and specific provisions of this IRB approved protocol, the ethical principles that have their origin in the Declaration of Helsinki, U.S. FDA requirements, including Good Clinical Practice (GCP), and all applicable local, state and federal regulations.

NOTE: The confidential information in the following document is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and applicable Institutional Review Board. By accepting this document, you agree that the information contained herein will not be disclosed to others without written authorization from Cognoa, Inc. except to the extent necessary to obtain informed consent from those persons to whom the device will be administered.

Protocol Signature Page – Principal Investigator

Study Title: Cognoa ASD Diagnosis Aid Validation Study

Protocol Version 3.0, Dated February 3, 2020

I have received and read the protocol dated **February 3, 2020** and agree to adhere to the requirements. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or informed consent form must first be approved by Cognoa, Inc. and the Institutional Review Board, except those changes necessary to eliminate apparent immediate hazards to subjects. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding their role in the study. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements, and with the reviewing Institutional Review Board (IRB) requirements. I agree to commence this study only after documented IRB approval is obtained.

Principal Investigator: _____ _____
Signature Date

_____
Printed Name

Table of Contents

Abbreviations

ADHD:	Attention Deficit Hyperactivity Disorder
ADI-R:	Autism Diagnostic Instrument Revised
AE:	Adverse Event
AGRE:	Autism Genetic Resource Exchange
ASADE:	Anticipated Serious Adverse Device Effect
ASD:	Autism Spectrum Disorder
ASRS:	Autism Spectrum Rating Scales
BRIEF:	Behavior Rating Inventory of Executive Functions
CFR:	Code Federal Regulation
CRF:	Case Report Form
DSM-5:	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FDA:	Food and Drug Administration
GCP:	Good Clinical Practice
HCP:	Healthcare Provider
HIPAA:	Health Insurance Portability and Accountability Act of 1996
ICH:	International Conference on Harmonization
IRB:	Institutional Review Board
JAMIA:	Journal of the American Medical Informatics Association
M-CHAT-R:	Modified Checklist for Autism in Toddlers-Revised
NPV:	Negative Predictive Value
PII:	Personally Identifiable Information
PPV:	Positive Predictive Value
SAE:	Serious Adverse Event
SRS:	Social Responsiveness Scale
USADE:	Unanticipated Serious Adverse Device Effect

Glossary

Term	Definition
Accuracy (error rate)	Rate of correct (incorrect) predictions made by the model over a data set. Accuracy is usually estimated by using an independent test set that was not used at any time during the learning process.
ADI-R	The Autism Diagnostic Interview-Revised (ADI-R) is a structured interview conducted by an experienced clinical interviewer questions a parent or caretaker who is familiar with the developmental history and current behavior of the individual being evaluated and uses standardized procedures to code the responses. The interview can be used to assess children and adults as long as their mental ages are two years or higher. Because the ADI–R is an interview rather than a test, and because it focuses on behaviors that are rare in non-affected individuals, it provides categorical results rather than scales or norms.
ADOS	The Autism Diagnostic Observation Schedule (ADOS) is a semi- structured assessment of communication, social interaction, and play (or imaginative use of materials) for individuals suspected of having autism or other pervasive developmental disorders. Its goal is to provide standardized contexts in which to observe the social-communicative behaviors of individuals across the life span in order to aid in the diagnosis of autism and other pervasive developmental disorders. Administration and coding are highly standardized. Therefore, valid assessment requires training.
Aid to Diagnosis	Output that provides a Healthcare Provider (HCP) information that *drives* a diagnosis. An Aid to Diagnosis is *not* a standalone diagnosis tool.
Algorithm	A process or set of rules to be followed in calculations or other problem-solving operations, especially by a computer. The Device has an underlying algorithm based on machine learning techniques that provides the output to the provider.
ASD	Autism Spectrum Disorder
Caregiver	The caregiver is often the parent of the child presenting ASD symptoms but may represent the legal guardian or adult in charge of the child's well-being and healthcare decisions.
Clinical reference standard	Best available method for establishing a subject's true status with respect to a target condition.
(Machine learning) Classification	Process of predicting to which predefined category (or class/label) a new observation belongs, on the basis of a training set of data containing observations whose category membership is known.
Classifier	Algorithm that evaluates unlabeled data and classifies them.

Term	Definition
Cognoa Research App	A smartphone-based app that describes the Cognoa device, provides guidance on and access to assessments and video software, and serves as a collection mechanism for assessments and videos.
Coverage	Proportion of a data set for which a classifier makes a prediction.
Diagnostic Output	Output from the Cognoa Device that is used as part of an overall diagnosis decision.
Dropout	After consenting to participation in trial (and therefore enrolling), a study subject discontinues participation in the trial (e.g., due to lack of interest, medical condition, adverse event). Dropout may simply be lost to follow up.
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; a guide to clinicians for diagnosis of neurobehavioral and psychiatric disorders.
Endpoint	Key outcome measure in a clinical study.
Feature	Individual measurable property or characteristic of an observation.
Futility	Situation in which proceeding further with a trial is not safe, feasible, or warranted from a statistical perspective. Studies can be stopped early due to unacceptable safety or risk/benefit profile, inability to recruit or perform study procedures, overwhelming early efficacy, or statistical impossibility of achieving endpoint(s).
HCP	Healthcare provider.
IC / ICF	Informed consent / Informed consent form.
IRB	Institutional review board.
Negative Predictive Value	Probability that a child identified by the device as Negative for ASD truly doesn't have ASD NPV = (True Negative)/ (True Negative + False Negative)
Positive Predictive Value	Probability that a child identified by the device as Positive for ASD truly has ASD PPV = (True Positive)/ (True Positive + False Positive)
Prevalence	Number of cases in a defined population at a single point in time, regardless of when they first developed the condition. Prevalence = (# of cases in sample with condition) / (total # of cases in sample)
Screening tool	A tool used in assist in clinical triage.

Term	Definition
Sensitivity	Measure of the proportion of children truly having ASD who are correctly identified by the device as Positive for ASD (or True positive rate). Sensitivity = (True Positive)/ (True Positive + False Negative)
Specificity	Measure of the proportion of children truly not having ASD who are correctly identified by the device as Negative for ASD (or True negative rate). Specificity = (True Negative)/ (True Negative + False Positive)
Specialist Clinician	Board-certified child adolescent psychiatrists, child neurologists, developmental-behavioral pediatricians, or psychologists, and have at least five years of experience in diagnosing and treating individuals with ASD.
Standalone/ primary diagnostic device	A device that outputs a primary diagnosis that is intended to be the sole source of input into clinical-decision making, absent any interaction with a clinician.
Standard of care	Current practice of care
Video Analyst	A trained healthcare professional who reviews Module 2 (Video Analysis module) videos submitted by caregivers to provide responses on the patient's behaviors and actions.

Protocol Summary

Title	Cognoa ASD Diagnosis Aid Validation Study
Sponsor	Cognoa, Inc.
Study Description	This study seeks to evaluate the ability of the fourth generation Cognoa ASD Diagnosis Aid (the "device") to aid healthcare providers in diagnosing autism spectrum disorder (ASD). Children age ≥18 to <72 months for whom the caregiver or a healthcare provider has concern regarding developmental delay will be assessed with the device in a prospective, blinded, multi-site, active comparator, cohort study. The output of the device will be compared to a specialist clinician diagnosis based on DSM-5 criteria, validated with independent review by one or two central specialist clinicians. For enrollment into the study, informed consent will be obtained from the subject's legal guardian. The subjects' caregivers will complete a caregiver assessment and upload two brief videos of the child for analysis prior to their evaluation by a specialist clinician. All participants, subjects' caregivers and HCPs, will be blinded to the results of the device. Furthermore, the caregivers, device video analysts, and HCPs providing inputs to the device algorithm will be blinded to each other's input.
Objective	To assess the ability of the device to aid in the diagnosis of ASD by comparing its diagnostic output with the clinical reference standard, consisting of a diagnosis made by a specialist clinician, based on DSM-5 criteria and validated by one or more reviewing specialist clinicians.
Endpoints	Primary: ● Achievement of a composite of positive predictive value (PPV) greater than 65% and negative predictive value (NPV) greater than 85% for the device in relation to the clinical reference standard in the overall study population. ● Measurement of the proportion of children for whom the Device provides no result. Secondary: ● Sensitivity of the device in relation to the clinical reference standard in the overall study population. ● Specificity of the device in relation to the clinical reference standard in the overall study population.
Safety Assessment	Adverse events (AEs) and serious adverse events (SAEs) will be collected and reported

Study Design	This is a multi-site, prospective, blinded, active comparator cohort study
Exempt Device Study	This study is exempt from the requirements of the IDE regulations (21 CFR 812.2 (c)), with the exception of 21 CFR 812.119 Disqualification of a Clinical Investigator. In accordance with 21 CFR 809.10(c), the device labeling shall include the following statement: "For Investigational Use Only. The performance characteristics of this product have not been established."
Number of Sites	The study will be conducted at up to 30 clinical sites within the United States.
Principal Investigator	To be determined
Study Sample Size	Up to 725 subjects
Subject Population	Female and male subjects between the ages of ≥ 18 months of age and < 72 months of age from a general population for whom a caregiver or healthcare provider has a concern about developmental delay.
Inclusion/Exclusion Criteria	Inclusion Criteria: ● Caregiver must be able to read, understand and sign the Informed Consent Form (ICF). ● Caregiver or HCP concern for developmental delay. ● Female or Male, ≥18 to <72 months of age. ● Functional English capability in the home environment. ● Caregivers must have smartphone capabilities for downloading the Cognoa Research App (Cognoa supports iOS 10.0 and up, Android 6.0 and up). ● Participants must be willing to be videotaped as part of the diagnostic assessment by the specialist clinician. Exclusion Criteria: ● Subjects with a prior diagnosis of ASD rendered by a healthcare professional. ● Subjects with suspected auditory or visual hallucinations or with prior diagnosis of childhood onset schizophrenia. ● Subjects with deafness or blindness. ● Subjects with known physical impairments affecting their ability to use their hands. ● Subjects with major dysmorphic features or prenatal exposure to teratogens (such as fetal alcohol syndrome). ● Subjects with history, suspicion, or diagnosis of genetic conditions (such as Rett's Syndrome or Fragile X) ● Subjects with microcephaly. ● Subjects with history or prior diagnosis of epilepsy or seizures. ● Subjects with a history of neglect.

	● Subjects with a history of brain malformation, injury or insult requiring interventions such as surgery or chronic medication. ● Subjects whose age on the date of enrollment is outside the target age range. ● Subjects or caregivers who have been previously enrolled in any Cognoa clinical study or survey. ● Subjects whose medical records had been included in any internal Cognoa training or validation sets.
Planned Schedule	First subject enrolled: August 2019
Study Duration	10 Months
Duration of Subject Participation	The duration of each individual subject's involvement in the study will be approximately 6 weeks.
Investigational and Control Diagnoses	Investigational: Cognoa device diagnostic output. Comparator: Specialist clinician diagnosis of ASD, validated by one or more central reviewing specialist clinicians.
Randomization	None. All subjects will be scheduled to undergo both investigational and comparator diagnosis for ASD.

1 BACKGROUND INFORMATION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that affects communication and behavior.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a guide created by the American Psychiatric Association and used by health care professionals to diagnose mental disorders, ASD primarily consists of persistent deficits in social communication and social interaction as well as the presence of restricted, repetitive patterns of behaviors, interests, and/or activities that can persist throughout life.

ASD is said to be a "developmental disorder" because symptoms generally appear in the first two years of life and is known as a "spectrum" because there is a wide variation in the type and severity of symptoms people experience.

Symptoms can include poor eye contact, difficulty reading social cues, failure to develop peer relationships, lack of social or emotional reciprocity, delayed speech development, difficulty sustaining conversations, lack of make-believe play, repetitive motor mannerisms, rigid adherence to routines, restricted interests and hyper- and/or hypo sensitivity to sensory input. ASD can have a significant impact on a child's day-to-day functioning including but not limited to impairments in communicating and getting needs met as well as difficulties with activities of daily living such as eating, dressing, playing, and sleeping.

Reported prevalence rates have been rising steadily since the 1960s and Autism Spectrum Disorders have risen to the top of childhood disorders with a prevalence rate of 1 in 59 children (Baio, Wiggins, Christensen et al., 2018). Multiple environmental, biologic, and genetic factors contribute to the development of ASD (Landrigan, 2010; Hallmayer, Cleveland, Torres, et al., 2011; Gaugler, Klei, Sanders, et al., 2014; Pinto, Pagnamenta, Klei, et al., 2010). Also, ASD is reported to occur in all racial, ethnic, and socioeconomic groups, and is approximately 4 times as prevalent in boys than girls.

As recognized by the Center for Disease Control (CDC), diagnosing ASD can be difficult, since there is no medical test, like a blood test, to diagnose the disorder. Healthcare professionals typically diagnose ASD by observing how the child talks and acts in comparison to other children of the same age and by asking questions to caregivers. They use the standardized diagnostic criteria for ASD provided in the American Psychiatric Association's Diagnostic and Statistical Manual, Fifth Edition (DSM-5) and focus on the assessment of a behavioral phenotype, including deficits in social communication, social interactions, and restricted or repetitive behaviors while also considering the developmental history as well as the alternate developmental diagnosis that would explain the symptoms.

The American Academy of Pediatrics recommends children be screened specifically for Autism at 18 and 24 months, or whenever caregivers express concern. The standard practice for screening is the Modified Checklist for Autism in Toddlers-Revised (M-CHAT-R). Many studies show, however, that primary HCPs are not screening children for ASD per these recommendations due to lack of confidence in the tools and/or lack of time to properly

review results with caregivers (Carbone et. al, 2016). If a primary care provider does suspect a developmental delay such as ASD, children are often put on watchful waiting until the clinician can be more certain of a problem. Moreover, in cases in which a referral for an assessment by a specialist is eventually provided, families may wait as long as 18 months between initial screening by their primary HCP and final diagnosis by the specialist, or even longer if the family is part of a minority population or lower socioeconomic group (Begeer, Bouk, Boussaid, Terwogt, & Koot, 2009). On average, the overall delay between first concerns arising in caregivers and an ASD diagnosis is approximately 3 years (Zuckerman, Lindly, & Sinche, 2015).

This delay in obtaining a diagnosis directly translates into delays in initiating early behavioral intervention. Such early intervention in ASD has been shown to have significant positive impact on a child's development, especially when delivered before 36 months (Warren et al., 2011).

Although families report concerns to their child's physician as early as 1 year of age, the average age of diagnosis in the United States is 4.4 years old and an estimated 27% of children with ASD still remain undiagnosed at 8 years of age. At later stages in development, many of the early intervention opportunities have passed. Delayed therapies are much less effective, and the delay can impact child learning and development creating lifelong disability, not to mention the related increased economic costs on caregivers and society (Dawson et al, 2009; Cidav, et al., 2017). Thus, there is a critical need to provide primary HCPs not only with tools to screen and triage children for ASD, but also tools that can provide them with higher levels of diagnostic certainty than are currently available in the primary care setting, thus enabling them to render a diagnosis without referral to a specialist.

Currently there are no FDA cleared or approved medical devices intended to aid in the diagnosis of ASD. Behavioral instruments with the highest diagnostic validity, such as the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and the Autism Diagnostic Instrument Revised (ADI-R) (Lord, Rutter, & Couteur, 1994) are typically delivered in a secondary care setting and can take several hours to administer by a trained specialist. The geographic and logistical hurdles in finding a healthcare professional trained to administer these instruments, the long duration of the standard exams, as well as the need for administration in a clinical facility, contribute to delays in diagnosis and an imbalance in coverage of the population needing attention (Shattuck PT, Durkin M, *et al*. 2009).

Rural communities face even more significant challenges regarding the availability of diagnostic specialists and geographic distance and transportation challenges, which results in delayed diagnosis of ASD, and consequently lower outcomes for children in these communities (Antezana, Scarpa, Valdespino, Albright, & Richey, 2017).

To address these challenges, Dr. Dennis Wall (scientific founder of Cognoa), then at the Center for Bioinformatics at Harvard Medical School, used machine learning techniques to create a 7- question classifier, which stems from machine learning research on answers to elements in the ADI-R, an interviewer-based examination administered by a trained clinician to a parent or care provider about autism symptoms, which can take between 2 and 5 hours to complete. Dr. Wall's Lab used data from Autism Speaks' Autism Genetic Resource Exchange (AGRE) to create the classifier and then used this same database, in addition to two independent sources (a collection of 1654

autistic individuals from the Simons Foundation and a collection of 322 autistic individuals from the Boston Autism Consortium), to show a high level of statistical accuracy in correctly classifying children with ASD. The classifier was 92% accurate in identifying those who do not have ASD (Wall, Dally, Luyster, Jung, & DeLuca, 2012).

Dr. Wall and his colleagues continued to apply the techniques of machine learning to each of the observational modules of the ADOS. The ADOS is a semi-structured observational tool administered by a trained clinician that is focused on first-hand observations of the child. The ADOS module that is administered is determined by the child's level of language (i.e. nonverbal, single words, phrased speech, fluent speech). By generating classifiers for each of the modules separately, Dr. Wall was able to adjust the risk generator to accommodate children across the developmental spectrum. He was able to again validate his findings in independent samples and showed a high degree of sensitivity and specificity in these archival datasets (Duda, Kosmicki, & Wall, 2014; Kosmicki, Sochat, Duda, & Wall, 2015).

Building on the work of Dr. Dennis Wall, Cognoa has further developed the algorithm/software to render a risk assessment for Autism. Cognoa's first-generation algorithm, developed in 2015 for screening purposes, showed better accuracy across a broader age range than other screening tools in a clinical study published in Autism Research (Kanne, Carpenter, & Warren, 2018). Cognoa has continued to advance the development of its machine learning platform as the basis for a reliable diagnostic device to improve the timeliness of autism diagnosis within the critical early childhood years (Abbas H., Garberson F., Glover E., Wall D. 2018).

2 STUDY DEVICE DESCRIPTION

The Study Device ("Device") is intended to aid healthcare providers in diagnosing Autism Spectrum Disorder (ASD) for children ≥ 18 months of age and < 72 months of age who are at risk for developmental delays based on a parental or healthcare provider concern.

The device is not intended for use as a stand-alone diagnostic device. It is intended to be used in conjunction with the clinical presentation of the patient.

The Device comprises of the following:

- A caregiver facing mobile application (Cognoa Research App)
- A Video Analyst Portal
- Healthcare Provider Assessment
- Underlying machine learning algorithm that drives the Device outputs ("Algorithm")

The Algorithm operates on information and data from three modules, that serve as data input.

Device Module	Module Description	Delivery System
Module 1 - Caregiver Assessment	Answers to questions on key developmental behaviors (by age group), provided by the child's caregiver.	Caregiver responses will be submitted via Cognoa Research App
Module 2 - Patient Video Analysis	Information provided by trained video analyst who reviewed videos of the child's natural play, communication, and social behavior at home, provided by the child's caregiver.	Caregiver will submit videos via Cognoa Research App Video analysts will access, review, and provide information via Video Analyst Portal
Module 3 - Healthcare Provider Assessment	Answers to questions on key developmental behaviors (by age group), provided by the child's healthcare provider.	Healthcare provider responses will be captured on a form via pen and paper. Study Staff data entry personnel will enter information from form into a study database.

The device evaluates the data inputs based on key developmental behaviors that are most indicative of autism and provides the following outputs -- Positive for Autism Spectrum Disorder (Positive ASD) or Negative for Autism Spectrum Disorder (Negative ASD). The device output will be recorded by Sponsor in a dedicated study data repository. It will not be shared with the referring HCP, caregivers, or specialist clinicians performing diagnosis and review.

3 STUDY OBJECTIVES

This study seeks to evaluate the ability of the device to aid in the diagnosis of ASD by comparing its diagnostic output with the clinical reference standard, consisting of a diagnosis made by a specialist clinician, based on DSM-5 criteria and validated by one or more reviewing specialist clinicians.

This is a multi-site, prospective, blinded, active comparator, cohort study in up to 725 subjects, ages ≥ 18 months of age and < 72 months of age.

4 STUDY ENDPOINTS

4.1 Effectiveness endpoints

The primary endpoints of this study are:
(1) to achieve a composite of positive predictive value (PPV) greater than 65% and negative predictive value (NPV) greater than 85% for the device in relation to the clinical reference standard in the overall study population, and
(2) measurement of the proportion of all children for whom the Device provides no result.

The secondary endpoints are:
(1) sensitivity of the device in relation to the clinical reference standard in the overall study population and
(2) specificity of the device in relation to the clinical reference standard in the overall study population.

4.2 Safety endpoints

Adverse events (AEs) and serious adverse events (SAEs) will be collected and reported from enrollment (informed consent signature) through completion of the reference diagnosis clinic visit.

5 STUDY DURATION

The study is expected to last 6 months. Subjects' participation in the study is expected to last 6 weeks.

6 STUDY DESIGN AND PROCEDURES

Primary healthcare providers who identify children at risk for developmental delay or learn of caregiver concern about developmental delay will inform caregivers about the clinical study. Caregivers may have access to a research coordinator, study website, or app (Cognoa Research app) to learn more about the study, provide consent, determine whether their child qualifies, and answer questions to test their comprehension of the study.

All subjects will undergo investigational (Cognoa assessment) and comparator diagnostic assessments for ASD using DSM-5 criteria and validating central review. Caregivers will be instructed to download the Cognoa Research app on their smartphone, set the username and password, complete a caregiver assessment about the child's behavior and development, and record two brief videos of their child. Caregivers will be given guidance on how to record videos. Both the assessment and the videos will be submitted via the Cognoa Research app. Cognoa video analysts will analyze the videos. The primary healthcare provider (HCP) will also answer an assessment about the child's behavior and development. The caregivers, video analysts, and HCPs providing inputs to the device algorithm will be blinded to each other's input.

Once the caregiver assessment, primary HCP assessment, and scored videos have been submitted, the device will generate a diagnostic output. The device output will be recorded by the Sponsor in a dedicated study data repository. The device inputs and the device output will not be shared with the referring HCP, caregivers, or

specialist clinicians performing diagnosis and review.

After the caregiver assessment has been completed and scorable videos submitted, the caregiver will be contacted by a research coordinator to schedule an appointment for a diagnostic evaluation by a specialist clinician. The specialist clinician will meet with the child and caregiver(s), conduct an assessment (which will be captured on video), and make a diagnosis of positive for ASD or negative for ASD based on DSM-5 criteria. The outcome of the diagnostic encounter may not be "uncertain" or "unknown at this time". The diagnosing clinician will also complete a standardized medical history and physical form (See Appendix), which may be completed during the diagnosing clinician visit. The standardized form and video will be sent to the Cognoa study monitor.

Determination of clinical diagnosis for study analysis purposes (**clinical reference standard**) will consist of a specialist clinician diagnosis by DSM-5 criteria, validated with independent review by one or two central specialist clinicians. After the diagnosing clinician has completed the patient assessment, the patient case is reviewed by one reviewing specialist clinician (who is provided with the standardized medical history and physical form, and a video of the diagnostic encounter). The diagnosing clinician will be instructed to not state any diagnostic conclusion, decision on any particular component of DSM-5 criteria, or diagnostic observation during the video of the assessment. If the assessment of the reviewing specialist clinician agrees with that of the diagnosing clinician, the diagnosis is considered validated and no further validation is conducted. If the reviewing specialist clinician disagrees with the diagnosing clinician, then the case is referred to a second reviewing specialist clinician. The study monitor will track reviewing clinicians' assessment results, maintaining blinding to all parties. The diagnosis for study analysis purposes is taken as the majority assessment of the three specialists (one diagnosing specialist and two reviewing specialists).

Subjects Identification and Recruitment

If the primary HCP has identified a child at risk for developmental delay or learns of caregiver concern about developmental delay the primary HCP or a member of his or her clinical team will inform caregivers about the study. Caregivers will be provided with material(s) describing the study and how to learn more and enroll. Caregivers may be enrolled in the study by Study Staff, if available at the site, via a website, or the Cognoa Research app. If caregivers have questions, they can direct them to their primary HCP or his/her staff assisting in the study. They can also contact the Sponsor's representative for the study. If the caregivers wish to pursue enrollment for their child, they will answer questions to determine if the inclusion/exclusion criteria are met. This will determine eligibility of the child for the study.

Process of Consent

The caregivers of the child will be given access to the consent form. The objective of the informed consent form is to ensure that they understand the purpose of the study, the risks and benefits of participating and the voluntary nature of their participation. If they have questions, they may reach out to their primary HCP, other research staff at the site, or the Sponsor's study coordinator. A child will not be enrolled in the study if his/her caregivers do not sign the consent. Child assent is not needed as the child involved will be less than 6 years old. Study subjects can end their participation in the study at any time.

Randomization

No randomization is necessary. This is a cohort single-arm study, with all subjects scheduled to undergo both investigational (Cognoa assessment) and diagnostic assessment for ASD using DSM-5 criteria and validated by one or two reviewing specialist clinicians.

Study Flow

Caregivers of subjects who have enrolled in the study will be instructed to download the Cognoa Research app, if they have not already done so, onto their smartphone, set a username and password, complete the caregiver assessment, and record two brief videos of their child for the video analysis portion of the assessment. Both the caregiver assessment and videos will be submitted via the Cognoa Research App.

The videos will be uploaded securely to a HIPAA secure server. Each submission will be scored by analysts who evaluate behaviors observed by answering a series of multiple-choice questions evaluating phenotypic features of ASD (e.g., on-verbal and verbal communication; social interaction; unusual sensory interests/reactions; stereotyped or repetitive motor movements, use of objects, or speech) on the combinative videos.

The videos analysts scoring the videos submitted for study purposes will have at least a Master's Degree from professional backgrounds including psychology, occupational therapy, physical therapy, speech-language pathology, special education, or a related field with specific training in autism diagnosis and/or treatment. They will also have at least 5 years of professional and/or clinical experience working with children with ASD. They will be trained, qualified to score the videos and their performance will be monitored according to Cognoa's procedures.

The video analysts will not have access to the caregiver assessment or the primary HCP assessment. If the videos are not scorable (e.g., if one or more videos are unhelpful for any reason such as: poor lighting, poor video or audio quality, bad vantage point, child not present or identifiable within a group, insufficient interaction with the child), the caregiver will be asked to submit additional videos. Caregivers will be allowed a maximum of 60 days from submitting the caregiver assessment (Module 1) to complete video upload or provide scoreable videos. Caregivers will be given guidance points on how to record videos.

Either during the primary care appointment when the patient was informed about the study or in a timely manner after the appointment, the primary care physician will answer the primary HCP assessment about the child's behavior and development. The clinician will only answer the assessment if the caregiver provides an initial consent. If the caregiver chooses not to participate in the study, the primary HCP assessment will be securely destroyed. The HCP will not have access to the responses in the caregiver assessment (Module 1), the patient videos, or the video's analysis (Module 2).

Once the caregiver assessment, primary HCP assessment, and scored videos have been submitted, the device will generate a diagnostic output. The device output will be recorded by Sponsor in a dedicated study data repository.

It will not be shared with the referring HCP, caregivers, or specialist clinicians performing diagnosis and review.

After the caregiver assessment has been completed and scorable videos submitted, the caregiver will be contacted by a research coordinator to schedule an appointment for a diagnostic evaluation by a specialist clinician. The subjects will be randomized to one of the specialist clinicians in the study at their respective site. The specialist clinician will meet with the child and caregiver(s), fill out a standardized form for medical history and physical information (and may ask caregivers to fill out parts of this form during the visit) (See **Appendix**), conduct an assessment, and make a diagnosis for ASD. He/she will utilize clinical observation, clinician interview and exam, medical record review, and assessment instruments as he or she deems necessary to arrive at a diagnosis based on DSM-5 criteria, positive for ASD or negative for ASD. The diagnosing specialist clinician will be provided with a standardized protocol to use for a portion of the recorded diagnostic encounter (this video is a unique video unrelated to the videos uploaded by the caregiver in the App (Module 2)). This recorded interaction includes standard approaches to eliciting behavior (e.g., asking child to blow bubbles or speak on toy phone). The diagnosing clinician will be instructed to not state any diagnostic conclusion, decision on any particular component of DSM-5 criteria, or diagnostic observation during the video of the assessment.

Any further diagnostic testing deemed necessary by the clinician will be included as part of the study records. Diagnosis of ASD alone or ASD plus co-morbid condition(s) would both constitute a positive for ASD clinical evaluation. If the clinician determines that the patient is negative for ASD and is able to arrive at a diagnosis other than ASD or determine that the patient is neurotypical, that data will also be captured.

The completion of diagnostic assessment by the diagnosing specialist clinician will indicate the conclusion of the subject's involvement in the study.

Determination of clinical diagnosis for study analysis purposes (clinical reference standard) will follow a staged sequential review, in which a specialist clinician diagnosis by DSM-5 criteria will be validated with independent review by one or two central reviewing specialist clinicians. The purpose of this approach is to mitigate against any excessive variability in the clinical diagnostic process. Specialist clinicians will be board-certified child adolescent psychiatrists, child neurologists, developmental-behavioral pediatricians, or psychologists, and will have at least five years of experience diagnosing autism spectrum disorder.

For clinical care purposes, at the end of subject participation in the study, any findings will be shared with the caregiver by the study site.

7 STUDY POPULATION

7.1 Study Subject Recruitment and Selection

This study will enroll up to 725 male or female subjects, between the ages of ≥ 18 months of age and < 72 months of age from multiple recruitment sites.

Subjects may also be recruited from the Investigator's existing patient database or from patients who present themselves to the study site requesting evaluation.

Only subjects who meet all eligibility criteria and who provide informed consent will be enrolled into the study.

Each subject will be evaluated by the primary HCP to assess his/her suitability for entry into the study according to the following inclusion and exclusion criteria.

7.2 Inclusion Criteria

To be included in the study, subjects must meet all of the following Inclusion Criteria:

- Caregiver must be able to read, understand and sign the Informed Consent Form (ICF).
- Caregiver or HCP concern for developmental delay.
- Female or Male, ≥18 to <72 months of age.
- Functional English capability in the home environment.
- Caregiver must have smartphone capabilities for downloading the Cognoa Research App (Cognoa supports iOS 10.0 and up, Android 6.0 and up).
- Participants must be willing to be videotaped during the diagnostic assessment by the specialist clinician.

7.3 Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following Exclusion Criteria:

- Subjects with a prior diagnosis of ASD rendered by a healthcare professional.
- Subjects with suspected auditory or visual hallucinations or with prior diagnosis of childhood onset schizophrenia.
- Subjects with deafness or blindness.
- Subjects with known physical impairments affecting their ability to use their hands.
- Subjects with major dysmorphic features or prenatal exposure to teratogens (such as fetal alcohol syndrome).
- Subjects with history, suspicion, or diagnosis of genetic conditions (such as Rett's Syndrome or Fragile X)
- Subjects with microcephaly.
- Subjects with history or prior diagnosis of epilepsy or seizures.
- Subjects with a history of neglect.
- Subjects with a history of brain malformation, injury or insult requiring interventions such as surgery or chronic medication.
- Subjects whose age on the date of enrollment is outside the target age range.
- Subjects or caregivers who have been previously enrolled in any Cognoa clinical study or survey.
- Subjects whose medical records had been included in any internal Cognoa training or validation sets.

7.4 Subject Number

If a caregiver completes the Informed Consent Form, meets the study eligibility criteria and is willing to participate, the subject will be assigned a study subject identification number.

This subject identification number will have no relation to Personally Identifiable Information (PII, defined as any data that could potentially identify a specific individual), such as date of birth, initials, medical record number, etc. All data transmitted and used for analysis will be identified by ID number and not subject identifying information.

7.5 Subject Discontinuation Criteria

If possible, every subject should remain in the study until completion of the required follow-up period. However, participation in this study is completely voluntary and a subject can choose to withdraw from the study at any time. Decision to withdraw will not affect or prejudice the subject's continued medical care in any way. In those instances, the investigator will attempt to obtain a final clinical assessment and an adverse device effect evaluation for the subject prior to this withdrawal. A subject will be considered lost to follow-up only after three unsuccessful, documented attempts to contact the subject have been made.

In addition, a subject can be discontinued for any of the following reasons: the Principal Investigator decides that continuing in the study would not be in the subject's best interest, a subject is noncompliant with the protocol, a subject has a serious reaction to the treatment, a subject develops any of the exclusion criteria during the study period or the study is stopped by the study sponsor.

8 DATA COLLECTION AND STORAGE

To maintain confidentiality, subjects will be assigned a unique subject ID number (see section 7.4 subject number), which will be used on all case report forms and linked to the Informed Consent Forms for audit and verification purposes. All data transmitted and used for analysis will be identified by ID number rather than subject-identifying information.

Authorized representatives of institutions participating in the study, the Food and Drug Administration (FDA), the Sponsor, and the reviewing IRB and other groups or organizations that have a role in this study will have access to and may view a subject's study information. They will be subject to regulations protecting patient confidentiality (e.g., HIPAA).

Data collection will be completed using electronic and/or paper report forms provided by the Sponsor, and data will be recorded into the Sponsor dedicated study data repository.

Data repository will include:

- Demographic information (child age, child biological sex, child race, child ethnicity, caregiver level of education)
- Device Inputs
  - Caregiver assessment
  - Video analysis
  - Primary HCP assessment
- Device Output
- Diagnostic assessment for ASD according to DSM-5 diagnostic criteria, by the diagnosing specialist clinician
- Medical, Developmental history and Physical
- Diagnostic review outcome of reviewing specialist clinicians

The data will be stored securely on an Amazon S3 cloud server with secured access and SSL encryption. Any data collected on paper will be kept in a secure and locked location at the primary HCP's or specialist clinician's office and periodically transferred to a central research coordinator at each site, before being recorded in an electronic format by the study staff and stored on a HIPAA-secure server.

All data will be retained for at least 7 years from the completion of the Study. Data collected on paper may be retained solely in electronic format.

9 ADVERSE EVENTS AND ADVERSE DEVICE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, device users or other persons, whether or not it is related to the investigational medical device. Expected Adverse Device Events (ADEs) may be previously identified in nature, incidence, severity or outcome in the study protocol, informed consent document, device operator manual, other risk analysis documentation or regulatory application.

9.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any adverse event, whether related to the use of an investigational device or clinical study device, that:

- led to a death;
- led to a serious deterioration in the health of the subject that:
  - resulted in a life-threatening illness or injury;
  - resulted in a permanent impairment of a body structure or body function;
  - required in-patient hospitalization or prolongation of existing hospitalization;

- resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function;

- led to fetal distress, fetal death or a congenital abnormality or birth defect.

9.1.3 Anticipated Serious Adverse Device Effect (ASADE)

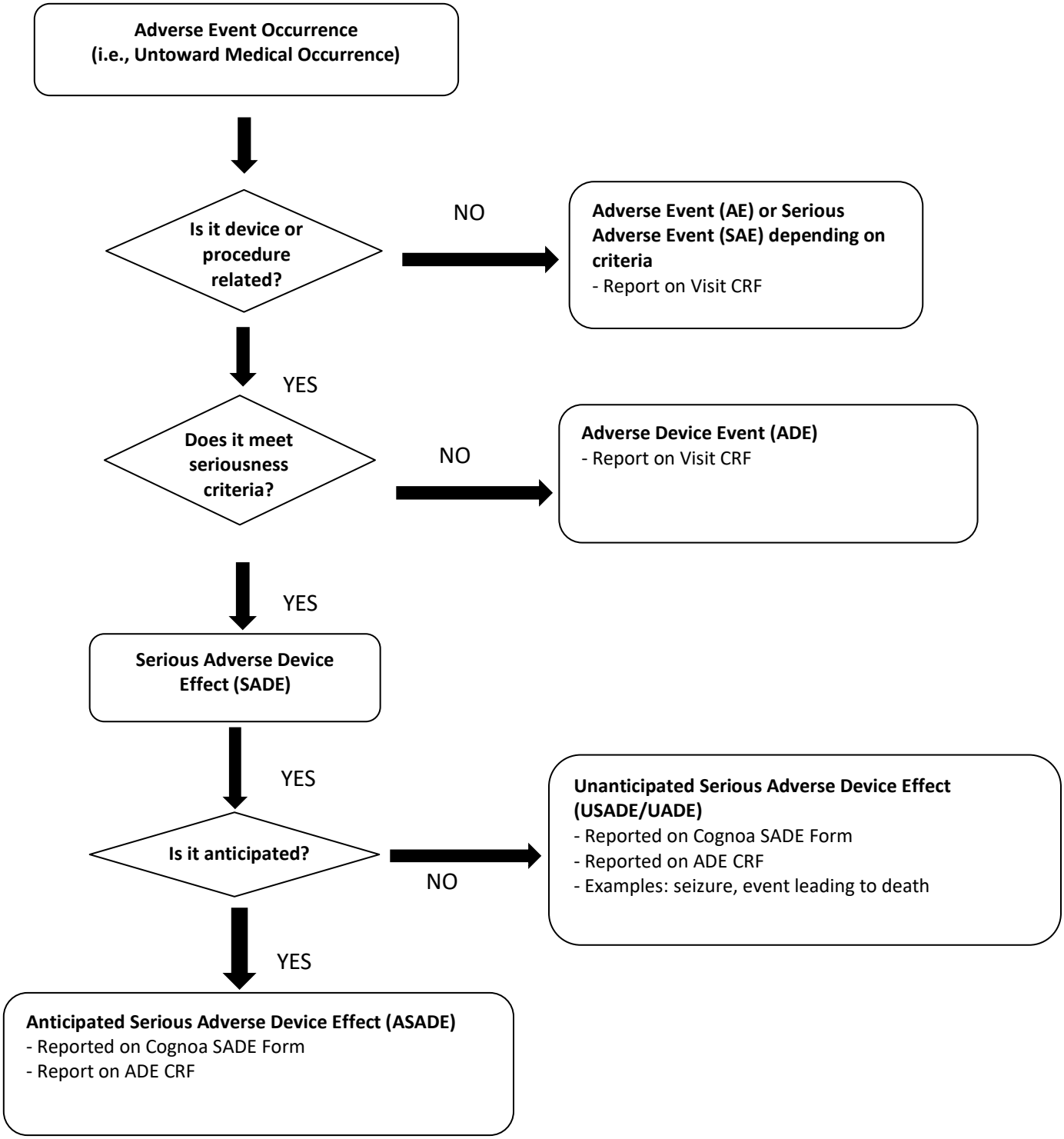
An anticipated serious adverse device effect (ASADE) is any SAE on health or safety or any life-threatening problem or death caused by, or associated with the device, if that effect, problem, or death was previously identified in nature, severity, or degree of incidence in the investigational plan, informed consent, operator manual, other risk analysis documentation or regulatory application; or any other serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.1.4 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is any SAE on health or safety or any life-threatening problem or death caused by, or associated with the device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, informed consent, operator manual, other risk analysis documentation, or regulatory application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

In subjects, the ADEs/SADEs include the effects related to the investigational medical device (clinical study device), or the procedures involved. For device users or other persons (other clinical staff in the treatment room) ADE/SADE is restricted to the effects related to investigational medical devices. ADEs/SADEs may include the effects (1) resulting from insufficient or inadequate instructions for use, deployment, installation, or operation, or any malfunction of the investigational medical device; or (2) resulting from user error or from intentional misuse of the investigational medical device.

Figure 1. Flowchart for classification of adverse device events



9.2 Recording AEs/ADEs and SAEs/SADEs

All AEs/SAEs or ADEs/SADEs will be: (1) evaluated and must be recorded in the subject's study case report forms (CRFs); (2) monitored and tracked from the time of the first treatment.

At each contact with the subject, the investigator must seek information on AEs/ADEs/SADEs by specific questioning and, as appropriate, by examination. AEs/ADEs/SADEs may be observed by the investigator and/or clinical research staff, elicited from the subject and/or family member or volunteered by the subject. All observed and volunteered adverse signs and symptoms, anticipated or unanticipated, regardless of severity or frequency, will be recorded in the case histories (medical chart and CRFs). Included in the description should be the nature of the sign or symptom, the date of onset, date of resolution (duration), the severity, anticipated or unanticipated, the relationship to study treatment or other therapy, the action taken (if any), and the outcome.

All SAEs/SADEs, anticipated or unanticipated, must be reported to Cognoa immediately but not later than 5 working days. The SADE must be recorded in: (1) the CRF and (2) a written report must be submitted to Cognoa within five (5) working days after the investigator first learns of the event and is to include a full description of the event and sequelae, in the format detailed by the Cognoa Serious Adverse Event Form.

9.3 Follow-up of Subjects after AEs

All reported AEs/ADEs/SAEs/SADEs should be followed until resolution or until the subject's participation in the study ends. Resolutions of AEs/ADEs/SAEs/SADEs are to be documented on the appropriate CRFs. All ADEs that result in permanent discontinuation from this clinical trial, whether serious or not, should also be reported on the subject Non-Completion of Study Form.

10 POTENTIAL RISKS / BENEFITS

10.1 Potential Risks

Risks related to the study are expected to be minimal.

There are no physical risks of participating in the study. However, one risk could be psychological. Caregivers may feel some discomfort in answering questions about their child's behavior. Children might also feel some discomfort being filmed for the video analysis.

Another potential risk is the possible release of sensitive medical, behavioral, or educational information. To mitigate the risk of releasing sensitive personal information, we adhere to confidentiality protocols to protect the privacy of personal information. When data is published, it is always anonymous and in a manner so that specific families or subjects cannot be identified.

10.2 Potential Benefits

The subjects may or may not benefit from the study.

Potential benefit is to identify subjects with ASD, thus enabling earlier therapy, which is known to positively impact long-term outcomes. All subjects in the study will receive an appointment with a specialist clinician, which is likely to occur in an expedited manner relative to their referral path were they not participating in the clinical study.

11 DATA ANALYSIS PLAN

11.1 Sample Size

This is a multi-site, prospective, blinded, active comparator study with up to 725 subjects who have been deemed appropriate for evaluation of the device.

11.2 Analysis Sets

The analysis set will include all enrolled subjects who complete assessment.

11.3 Statistical Analyses

Statistical analyses will be conducted per Statistical Analysis Plan version 1.4.6.

11.4 Safety Analyses

Device-related and procedure-related adverse effects (AEs) will be tabulated and analyzed.

12 STUDY MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

12.1 Investigator Selection

The Investigator(s) will be invited to participate in the study based on his or her medical specialty and experience conducting clinical research studies. Access to potential study subjects and the Investigator's sincere interest in this study along with expressed willingness to cooperate with the study process and requirements are also considered.

12.2 Training and Monitoring

The investigators and site research staff will be trained on the study procedures.

Investigator will allow sponsor representatives to periodically review the study documentation. Monitoring of the site will occur to evaluate the progress of the study, verify the accuracy and completeness of CRFs, assure that all protocol requirements, applicable FDA regulations and the investigator's obligations are being fulfilled and resolve any inconsistencies in the study records.

12.3 Informed Consent

The investigator is responsible for ensuring that informed consent, using an Institutional Review Board (IRB) approved informed consent document, is obtained for each subject before the performance of any protocol procedures, including administration of the study device. The informed consent document must comply with all essential elements as defined in 21 CFR 50.25 "Elements of Informed Consent" and must contain a statement that consent is freely given, the study involves research, the subject is aware of the risks and benefits of entering the study, and that the subject is free to withdraw from the study at any time. An evaluation of each candidate will be conducted by the investigator. Upon determining a subject's eligibility status, the subject will be offered the opportunity to participate in the study.

The investigator or the investigator's designee will inform all subjects regarding the purpose of the study and expected duration, as well as the potential risks and benefits that may result from participation. The subjects shall be informed by the investigator or investigator's designee that they are free to refuse participation in this clinical study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

The acquisition of informed consent will be documented in the subject's medical records, as required by 21 CFR 812.140.

12.4 Protocol Compliance

The principal investigator must comply with all terms of the protocol.

12.5 Protocol Amendments

Neither the principal investigator nor the sponsor will modify or alter this protocol without first obtaining the concurrence of the other party (with the exception of amendments which involves mitigating a medical emergency or immediate health risk to the subject). The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the sponsor and the principal investigator. IRB approval must be obtained before implementation of an amendment.

12.6 Protocol Deviation

Significant protocol deviations must be reported to the IRB according to their policies.

12.7 Study Discontinuation

Cognoa, Inc. (the sponsor) has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following: incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects; subject enrollment is unsatisfactory; number of protocol deviations is unacceptable; data recording is inaccurate or incomplete; or questionable study site compliance with ICH-E6, Good Clinical Practice.

12.8 Data Collection, Record Keeping and Storage

The principal investigator is responsible for assuring that all study records including case report forms (CRFs), informed consent forms, device accountability records, source documents (e.g., notes, medical records etc.) and other study records are complete, accurate and recorded in a timely manner. All study data will be captured on the CRFs. All data entries on the CRFs will be recorded completely, promptly, and legibly using blue or black indelible ink pen and accuracy will be ensured. The corrections on CRFs will be made only by the designated study staff. To make a correction to an entry, the data will be crossed through with a single line (the original entry should be visible) and then will be initialed and dated by the person making the correction.

The study records will be maintained in a secure location throughout the duration of the study. Upon study completion or termination, records will be kept at a secure location until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

12.9 Subject Confidentiality

This study preserves the confidentiality of all subjects under the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule. The following safeguards will be in place to protect the privacy of the individuals who are the subjects of the health information to be used in the research and the confidentiality of that information:

The subjects will be informed by the investigator or the investigator's designee that their medical records will be kept as confidential as possible but may be subject to review by: (1) Cognoa, or its representative; (2) reviewing

IRB; and/or (3) by appropriate regulatory bodies (e.g. the US Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies).

Only pieces of personal information required for purposes of the study will be collected. The personal information will be collected and used to ensure subject eligibility for study participation, to conduct the study and to assess the results of the study as required and permitted by law. Subjects have the right to see and copy any of the information gathered about them and request changes if the information is not correct, until it is no longer kept by the investigator. Permission to use or disclose personal information, except for that has been collected and relied on may be cancelled by the subject by written notice. If the subject is withdrawn from the study, the information collected to that time may still be used to preserve the scientific integrity of the study. There is no expiration date to this authorization.

Subjects' identities will be kept confidential. Subjects will be assigned a unique study code that will not reveal the subjects' identity, and this code will be used on all study documents.

12.10 Financial Considerations

Subject Compensation:

The subject's caregiver will be compensated for their participation, which is defined as completion of caregiver assessment, brief videos, and specialist clinician evaluation.

Costs to the Subject:

The specialist clinician evaluation is part of standard of care referral and should be covered by insurance. The costs not covered by subject's insurance will be covered by the sponsor, up to $1,000.00. Please note that genetic testing and/or neuroimaging will not be covered by the sponsor.

Clinician Compensation:

Referring primary care physicians will be compensated per HCP assessment they complete.
Specialist clinicians, who handle the primary diagnosis, will be compensated per patient visit.
Reviewing specialist clinicians will be compensated per independent review of cases.

REFERENCES

Abbas H., Garberson F., Glover E., Wall D. (2018). Machine learning approach for early detection of autism by combining questionnaire and home video screening. *Journal of the American Medical Informatics Association*, Volume 25, Issue 8, August 2018, Pages 1000–1007, https://doi.org/10.1093/jamia/ocy039

Antezana, L., Scarpa, A., Valdespino, A., Albright, J., & Richey, J. A. (2017). Rural Trends in Diagnosis and Services for Autism Spectrum Disorder. Frontiers in psychology, 8, 590. doi:10.3389/fpsyg.2017

Baio J, Wiggins L, Christensen DL, et al. (2018). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. MMWR Surveill Summ. 2018 Apr 27;67(6):1-23. doi: 10.15585/mmwr.ss6706a1.

Begeer, S., Bouk, S. El, Boussaid, W., Terwogt, M. M., & Koot, H. M. (2009). Underdiagnosis and referral bias of autism in ethnic minorities. *Journal of Autism and Developmental Disorders*, *39*(1), 142–148. http://doi.org/10.1007/s10803-008-0611-5

Carbone, P., Norlin, C., & Young, P. (2016). Improving early identification and ongoing care of children with Autism Spectrum Disorder. *Pediatrics,* 137(6) DOI**:** 10.1542/peds.2015-1850

CDC. (2014). *Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010*. Retrieved from http://www.cdc.gov/mmwr/pdf/ss/ss6302.pdf

Cidav Z., PhD, Munson J., PhD, Estes A., PhD, Dawson G., PhD, Rogers S., PhD, & Mandell D., ScD. (2017). Cost Offset Associated With Early Start Denver Model for Children With Autism. Journal of the American Academy of Child & Adolescent Psychiatry,56(9), 777-783. doi: 10.1016/j.jaac.2017.06.007

Dawson G., Rogers S., Munson J., Smith M., Winter J., Greenson J., Donaldson A., & Varley, J., Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model, Pediatrics, 2010;125;e17; originally published online November 30, 2009; DOI: 10.1542/peds.2009-0958

Duda, M., Kosmicki, J. a, & Wall, D. P. (2014). Testing the accuracy of an observation-based classifier for rapid detection of autism risk. *Translational Psychiatry*, *4*(8), e424. http://doi.org/10.1038/tp.2014.65

Kosmicki, J. a, Sochat, V., Duda, M., & Wall, D. P. (2015). Searching for a minimal set of behaviors for autism detection through feature selection-based machine learning. *Translational Psychiatry*, *5*(2), e514. http://doi.org/10.1038/tp.2015.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., … Rutter, M. (2000). *Autism Diagnostic Observation Schedule (ADOS)*. *Journal of Autism and Developmental Disorders* (Vol. 30). http://doi.org/10.1007/BF02211841.

Lord, C., Rutter, M., & Couteur, A. L. (1994). Autism diagnostic interview-revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685. http://doi.org/10.1007/BF02172145

Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L *et al*. Timing of identification among children with an autism spectrum disorder: findings from a population- based surveillance study. *J Am Acad Child Adolesc Psychiatry* 2009; 48: 474–483

Snow, A. V, & Lecavalier, L. (2008). Sensitivity and specificity of the Modified Checklist for Autism in Toddlers and the Social Communication Questionnaire in preschoolers suspected of having pervasive developmental disorders. *Autism : The International Journal of Research and Practice*, *12*(6), 627–644. http://doi.org/10.1177/1362361308097116

Wall, D. P., Dally, R., Luyster, R., Jung, J. Y., & DeLuca, T. F. (2012). Use of artificial intelligence to shorten the behavioral diagnosis of autism. *PLoS ONE*, *7*(8). http://doi.org/10.1371/journal.pone.0043855

Warren, Z., McPheeters, M. L., Sathe, N., Foss-Feig, J. H., Glasser, A., & Veenstra- Vanderweele, J. (2011). A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics*, *127*(5), e1303–e1311. http://doi.org/10.1542/peds.2011-0426

Witwer, A. N., & Lecavalier, L. (2007). Autism screening tools: an evaluation of the Social Communication Questionnaire and the Developmental Behaviour Checklist-Autism Screening Algorithm. *Journal of Intellectual & Developmental Disability*, *32*(3), 179–187. http://doi.org/10.1080/13668250701604776

Zuckerman, K. E., Lindly, O. J., & Sinche, B. K. (2015). Parental Concerns, Provider Response, and Timeliness of Autism Spectrum Disorder Diagnosis. *The Journal of Pediatrics*, 1–10. http://doi.org/10.1016/j.jpeds.2015.03.007

APPENDIX - STANDARDIZED MEDICAL HISTORY AND PHYSICAL FORM

HISTORY AND PHYSICAL INTAKE FORM

Subject ID	Date of Evaluation		Biological Sex ☐Female ☐Male
Child's Name (Last, First)	Date of Birth		Age (months)

HISTORY OF PRESENTING ILLNESS:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Age caregiver first became concerned about patient's development or behavior? _____

Does the child have any of the following compared to **other children his/her age (Circle all that apply)**:

Impulsive/Overactive	Destructive	Unable to separate from parent
Short attention span/Distractible	Aggressive	Sad or Depressed
Daydreams	Wetting pants/bed	Suicidal thoughts
Classroom disruption	Bowel accidents	Eats or Mouths non-food items
Is easily overstimulated in play	Poor eye-contact	Psychiatric/emotional problems
Easily frustrated	Low self-esteem	Plays with toys abnormally
Doesn't follow directions	Isolated/withdrawn	Sexualized behavior
Oppositional/Defiant	Excessive worry/fears	Obsessions or compulsions
Sensitive to noises/ lights/ textures	Need for sameness	Difficulty making or keeping friends
Self-injurious (head bangs, bites/hits self)	Requires a lot of parental attention	Overreacts when faced with a problem
Rocking/spinning/hand flapping	More interested in things than in people	Does not show much emotion

Other problems or comments regarding infancy or early childhood development?

_____

_____

_____

_____

_____

BIRTH HISTORY

<table>
<tr><td colspan="4">Is child adopted? ☐ Yes ☐ No In foster care? ☐ Yes ☐ No If Yes, from what age? _____</td></tr>
<tr><td>Mother's age during pregnancy</td><td>Father's age during pregnancy</td><td>Prenatal care received?
☐ Yes ☐ No</td><td>Previous pregnancies? ☐ No
☐ Yes: If yes, number of pregnancies ____
Number of miscarriages (if any): _____</td></tr>
<tr><td colspan="4">Prescription medications used during pregnancy:</td></tr>
<tr><td colspan="4">Maternal use any of the following while pregnant:

☐ Tobacco ☐ Alcohol ☐ Marijuana ☐ Methamphetamines ☐ Cocaine/Crack ☐ Heroin ☐ Methadone

☐ Other (specify): _____</td></tr>
<tr><td colspan="4">Were there any problems during pregnancy or delivery? ☐ No ☐ Yes (details):</td></tr>
<tr><td>Full term (40 wks)? ☐ Yes ☐ No</td><td>Birth weight:
_____(lbs)
Or
_____(kg)</td><td>Birth Length:
_____ (in)
Or
_____ (cm)</td><td>Birth Head Circ:
_____ (in)
Or
_____ (cm)</td></tr>
<tr><td colspan="3">If premature, how early? _____weeks

If overdue, how late? _____weeks</td><td>Method of Delivery:
☐ Vaginal
☐ C-section</td></tr>
<tr><td colspan="4">Did child need any special care after delivery? ☐ No ☐ Yes (details):</td></tr>
<tr><td colspan="4">Health problems (feeding difficulties, poor weight gain, etc.) during infancy?
☐ No ☐ Yes (details):</td></tr>
<tr><td colspan="4">Maternal or Paternal Depression following the birth?
☐ No ☐ Yes (details):</td></tr>
</table>

Additional Birth History:

DEVELOPMENTAL HISTORY:

Age of first developmental concern: months

Please note the age at which your child first did each of the following (write N/A if he/she does not do this yet):
Sat independently: _____ Walked 10 steps: _____
Said first word (other than mama/dada): _____ Put two words together (e.g. "my ball")_____
Toilet trained: Bladder _____ Bowel _____ Fed self with utensils (fork, spoon) _____

Provide an example of something your child might say:

Provide an example of how your child lets caregiver know what he/she needs?

Caregiver concern regarding child's ability to think or that learning is delayed?
☐ No ☐ Yes, Please specify:

How old does caregiver think child seems to act? _____

History of child gross motor delays (e.g. sitting, walking, skipping, riding a bicycle, etc.)?

☐ No ☐ Yes, Please specify:

History of child fine motor delays (e.g. drawing, writing, cutting, eating with utensils)? What any part of child's small muscle development slow?

☐ No ☐ Yes, Please specify:

Are child's self-help skills (i.e. dressing, toileting, bathing, etc.) age-appropriate?

☐ Yes ☐ No: Please explain:

Has child ever lost any previously acquired and well-established language, motor, self-help, or social skills? ☐ No ☐ Yes - What age? ____ years. Please describe:
Any prior developmental evaluations through Early Intervention, Developmental Pediatrics, etc.:

PAST MEDICAL HISTORY:

Circle Any That Apply

Chickenpox Frequent ear infections Problems with ears or hearing Nasal allergies Problems with eyes or vision

Asthma, bronchitis, bronchiolitis, or pneumonia Any heart problem or heart murmur Anemia or bleeding problem

Blood transfusion HIV Organ transplant Malignancy/bone marrow transplant Chemotherapy

Frequent abdominal pain Constipation requiring doctor visits Recurrent urinary tract infections and problems

Congenital cataracts/retinoblastoma Metabolic/Genetic disorders Cancer Kidney disease or urologic malformations

Sleep problems; snoring Chronic or recurrent skin problems (eg, acne, eczema) Frequent headaches

Convulsions or seizures Obesity Diabetes Thyroid or other endocrine problems High blood pressure

History of serious injuries/fractures/concussions Dental decay

Hospitalizations/ Major Illnesses /Surgeries:

SOCIAL HISTORY

Early Intervention Services: ☐ No Services ☐ Current Services (Please specify in hr/week or hr/ month):
Does the child currently attend daycare? ☐ No ☐ Yes (Please explain):

Current Grade in School (if applicable):	Type of Class (mainstream or special education services):
Concerns (if any) child's current teacher has?	
Any evaluations child has received through school district (SST, Speech Evaluation, Psychoeducational evaluation, etc.):	
Has child ever had an Individual Education Plan (IEP or IFSP)? ☐ No ☐ Yes. If yes, reason:	
Services child <u>CURRENTLY RECEIVES</u> at school and how often (*i.e., Resource support or specialized instruction, aide, speech therapy, occupational therapy, adaptive PE, social skills group, positive behavioral support plan, etc.*).	
Any other services child has <u>RECEIVED IN THE PAST</u> through school.	
Please describe any major family stressors at the present time, if any?	

Please note if there is a history of any of the following (check all that apply):

❒ Marital discord/separation/divorce	❒ Parent deployed overseas/out of town for work extensively	❒ Financial problems
❒ Custody disputes	❒ Parent legal problems	❒ Parent job loss
❒ Birth/Adoption of another child	❒ Parent alcohol/ drug use	❒ Witness physical violence
❒ Severe sibling/ illness or death	❒ Living away from parent	❒ Witness sexual abuse
❒ Parent emotionally/mentally ill	❒ Other significant trauma/negative event	

If yes to any of the above, provide circumstances:

_____

_____

_____

_____

REVIEW OF SYMPTOMS

Concern	Never	Currently	In the past
Fatigue			
Sleep problems (falling asleep, staying asleep, snoring, difficulty breathing at night, etc.)			
Genetic disorder			
Head injury/brain problem (hydrocephalus, brain bleed)			
Seizures			
Headaches			
Tics, tremors, or unusual movements			
Eye or vision problem			
Ear or hearing problem			
Dental or tooth problem			
Nose and Throat problems			
Heart problem			
Heart rhythm problems			

Concern	Never	Currently	In the past
Breathing/lung problem, asthma			
GI problem: vomiting/reflux/stomach pain			
Diarrhea (loose, watery stools)			
Constipation (hard, painful stools)			
Feeding problem or use of a feeding tube			
Limited diet (picky eater):			
Kidney/bladder/genital problems			
Bone, joint, or muscle problems			
Anemia or other blood problems			
Skin conditions or birthmarks			
Endocrine or hormone problems			
Growth problems (short stature, overweight/underweight, etc.)			
Allergies			
Health concern not listed above			

Child uses any adaptive equipment (circle)?

Glasses Hearing aids Walker Wheelchair Communication device

Other:

BIOLOGICAL FAMILY HISTORY

Please note who, if any, of the child's biological relatives have had these conditions ("blood related" family members only; i.e. biological parents, siblings, aunts, uncles, grandparents)

Conditions:	Relative(s) with the condition (if 2d degree relation, specify maternal or paternal)
Autism Spectrum Disorder	
ADHD	
Learning disabilities or intellectual disability	
School failure (please explain)	
Developmental delays (speech delay, delayed walking, etc.)	
Schizophrenia or psychosis	
Depression	
Bipolar Disorder	
Anxiety or OCD	
Tics or Tourette's Disorder	
Seizures	
Genetic disorder (Down Syndrome, Fragile X Syndrome, Tuberous Sclerosis Complex,, Neurofibromatosis, etc.)	
Substance abuse (alcohol, drugs, etc.)	
Other/Additional Details (Please Specify)	

Current medication(s) that child takes:

ALLERGIES:

❒ Not Known Medication Allergies

IMAGING, LABORATORY, AND NEUROPSYCHOLOGICAL TESTING

(attach reports if available, excluding/redacting assessment portion)

Test	Yes	Don't Know	If Yes, Abnormal?
Array CGH (microarray) or Karyotype			Details:
Fragile X			Details:
Testing for Rett Syndrome (MECP2)			Details:
Whole Genome/ Exome			Details:
MRI of the brain			Details:
EEG (electroencephalogram)			Details:
Sleep Study			Details:
Audiology (Hearing) Testing			Details:

Neuropsychological Testing			Details:
Other:			Details:

PHYSICAL EXAMINATION

Height: _____cm Weight: _____kg Head Circumference: _____cm
(attach growth charts if available)

CATEGORY	STATUS	IF ABNORMAL, DESCRIBE BELOW
Vital Signs	☐Normal ☐Abnormal ☐Not Examined	
General Appearance	☐Normal ☐Abnormal ☐Not Examined	
HEENT	☐Normal ☐Abnormal ☐Not Examined	
Respiratory	☐Normal ☐Abnormal ☐Not Examined	
Cardiovascular	☐Normal ☐Abnormal ☐Not Examined	

CATEGORY	STATUS	IF ABNORMAL, DESCRIBE BELOW
Abdomen	☐Normal ☐Abnormal ☐Not Examined	
Genitourinary	☐Normal ☐Abnormal ☐Not Examined	
Musculoskeletal	☐Normal ☐Abnormal ☐Not Examined	
Lymph Nodes	☐Normal ☐Abnormal ☐Not Examined	
Skin	☐Normal ☐Abnormal ☐Not Examined	

Neuropsychiatric: - Mental Status	☐Normal ☐Abnormal ☐Not Examined	Appearance/Behavior (e.g. level of motor activity, eye contact): Apparent reaction to situation/reactivity level to sensory stimuli: Speech/Language: Vocalization/speech production Affect (range of expressed emotions) Thought Processes: Thought Content: Cognition:
Neurological: - Cranial Nerves	☐Normal ☐Abnormal ☐Not Examined	
Neurological: - Tone, Motor & Coordination	☐Normal ☐Abnormal ☐Not Examined	Check if any abnormal movements noted: ☐ Tics ☐ Chorea ☐ Stereotypy

Neurological: - Reflexes	☐Normal ☐Abnormal ☐Not Examined	
Neurological: - Sensory	☐Normal ☐Abnormal ☐Not Examined	