Official Title: Study to Evaluate and Explore Scales for Repetitive and Restricted Behaviors and Digital Biomarkers in Children, Adolescents and Adults With Autism Spectrum Disorder (ASD)

NCT Number: NCT03611075

Document Date: Protocol Version 2: 24-April-2019

PROTOCOL

TITLE:	**STUDY TO EVALUATE AND EXPLORE SCALES FOR REPETITIVE AND RESTRICTED BEHAVIORS AND DIGITAL BIOMARKERS IN CHILDREN, ADOLESCENTS AND ADULTS WITH AUTISM SPECTRUM DISORDER (ASD)**
PROTOCOL NUMBER:	BP40331
VERSION NUMBER:	2
TEST PRODUCT:	NA
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 05 March 2018
DATE AMENDED:	Version 2: See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	24-Apr-2019 20:42:36

PROTOCOL ACCEPTANCE FORM

TITLE:	**STUDY TO EVALUATE AND EXPLORE SCALES FOR REPETITIVE AND RESTRICTED BEHAVIORS AND DIGITAL BIOMARKERS IN CHILDREN, ADOLESCENTS AND ADULTS WITH AUTISM SPECTRUM DISORDER (ASD)**
PROTOCOL NUMBER:	BP40331
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

PROTOCOL AMENDMENT, BP40331 VERSION 2
RATIONALE

RATIONALE FOR THE AMENDMENT

Protocol BP40331 has been amended to include the following changes:

- **Section 4.2.2; Section 5**: The addition of two typical developing cohorts (healthy participants) for the collection of digital biomarkers.

- **Section 5.1: Inclusion criteria #1** expanded the age range of participants, **#5 and #6** were rephrased to allow more flexibility for investigator to judge the proficiency in English language compatible with the study measurements.

- **Section 4.1.1; Section 5.4**: To prevent unnecessary screen failures not justified scientifically, a possible extension of the screening period up to 6 weeks was added in case of unexpected logistical issues to schedule Baseline.

- **Section 8.1.1**; Explanation about the purpose of review of audio recordings by Bracket was added. The audio recordings collected via rater station will be used for quality review only and no information about participant and families will be extracted.

- **Section 8.1.1.1**: Guidance on caregiver requirements for participants in residential homes was clarified. Because some participants with ASD and, in particular, participants with low IQ may be living in residential homes, specific guidance about caregiver requirements for such participants living in residential homes needed to be added

- **Section 8.1.1.2:** Guidance for administration of participant-reported scales to illiterate participants was clarified.

- **Section 8.1.1.3:** Clarification for administration of both the caregiver and participant-reported scale version “if deemed appropriate by Investigator” was clarified.

- **Appendix 1, Section 2.2**: Clarification on destroying and retention of audio recordings after study completion. Audio recordings will be stored for at least 15 years after study end. .

- Further changes to the protocol were made to align with the substantial changes specified above and improve consistency and clarity throughout the protocol. Also see Protocol Summary of Changes for details.

Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, BP40331 VERSION 2
SUMMARY OF CHANGES

1.1 Synopsis

The synopsis has been updated to reflect the changes to the protocol where applicable.

Table 2 Schedule of Activities for Collection of Digital Biomarkers. All participants (*typically developing* healthy participants and participants with ASD)

[…] Digital biomarkers will be collected from all participants, those with ASD and the *typically developing (TD)* healthy participants. […]

5. Final satisfaction surveys on the participant's experience about collection of digital biomarker will be completed by participants *and by caregivers*. […]

4.1 OVERALL DESIGN

[…] *Typically developing (TD) h*ealthy participants ~~(i.e., children of 5-12 years of age)~~ will be enrolled for validation of *digital* biomarkers only, see Table 2.

4.1.1 Length of the Study

[…]•Screening and run-in period: up to 4 weeks. *However, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of caregivers or raters), the screening period may be extended to up to 6 weeks.* […]

4.2.2 Rationale for Control Group

This study includes a group of *TD* healthy male and female ~~children~~ *participants (15 children* age~~d~~ 5 to 12 years*, 15 adolescents age 13 to 17 years, and 15 adults age~~d~~ 18 to 45 years* ~~(inclusive)~~. The *TD* healthy participants will be needed to compare and validate the digital biomarkers versus participants with ASD. The *TD* healthy control group will participate in collection of digital biomarker data (see *Schedule of Activities [*SoA*]* for digital biomarkers, Table 2) and except of the *Reading the Mind in the Eyes Test (*RMET*)* needed as anchor data for the analysis of digital biomarkers, no clinical scales will be performed in the *TD* healthy control group since these scales are not suitable for typically developed individuals (see main SoA, Table 1).

5. STUDY POPULATION

[…] The participants are children ~~from~~ *age* 5 *to* 12 years, adolescents ~~from~~ *age* 13 *to* 17 years, and adults age ~~from~~ 18 *to* 45 *years* ~~of age inclusive~~ who meet all diagnostic criteria of ASD according to the DSM 5 criteria (see Section 5.1). […]

- Age: children 5 *to* 12 years ~~old~~; adolescents 13 *to* 17 years ~~old~~ and adults 18 *to* 45 years ~~old~~

In addition, *45* ~~15~~ *TD* healthy participants (*15* children *age* 5 *to* 12 years ~~of age~~, *15 adolescents age 13 to 17 years,* ~~of age~~ *and 15 adults age 18 to 45 years* ~~of age~~) will be enrolled for validation of *digital* biomarkers only. See Section 9.1 (sample size justification) for further details. […]

5.1 INCLUSION CRITERIA

Participants with ASD and *TD* healthy participants are eligible to be included in the study only if all of the following criteria apply:

Inclusion criteria specific to *typically developing* healthy participants:

1. Male and female *TD* healthy participants age 5 to ~~12~~ *45* years inclusive.

Inclusion criteria specific to *typically developing* healthy participants and participants with ASD:

5. *English proficiency compatible with the study measurements as judged by the Investigator.*~~Participants who are fluent in English.~~

6. ~~Language, h~~*H*earing, ~~and~~ vision, *and speech* compatible with the study measurements as judged by the Investigator.

5.2 EXCLUSION CRITERIA

Participants with ASD and *TD* healthy participants are excluded from the study if any of the following criteria apply:

Exclusion criteria specific to *typically developing* healthy participants:

1. ~~Healthy~~ *Typically developing* healthy ~~children~~ *participants* with first degree relative with ASD.

Exclusion criteria specific to participants with ASD:

6. History of alcohol misuse and/ or illicit drug use during the last 12 months *prior to screening* ~~of the study~~.

5.4 SCREEN FAILURES

[…]*Screening assessments will be performed during the time window indicated in the SoA (see Section 1.2), i.e., within 4 to 2 weeks before the Baseline visit. However, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of caregivers or raters), the screening period may be extended to up to 6 weeks. Beyond 6 weeks the participant is considered a screen failure, but can be re-screened.*

5.5 RECRUITMENT PROCEDURES (*TYPICALLY DEVELOPING* HEALTHY PARTICIPANTS)

6.2.1 Permitted Therapy for Participants with ASD

Any medication or vaccine (including over the counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant from *12* ~~4~~ weeks prior to screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency). […]

6.2.2 Non-Pharmacological Interventions for Participants with ASD

Non-pharmacological interventions (e.g., subject psychotherapy, cognitive behavioral therapy, applied behavioral analysis [ABA], speech therapy, occupational therapy, rehabilitative therapy, and social skills training) must be stable for *6* ~~4~~ weeks prior to screening and must remain stable throughout the ongoing study in terms of type of intervention and intensity. […]

8.1.1 Clinical Outcome Assessments

[…]The sequence of assessments *specific for each age cohort* ~~will be~~ *is* pre-defined on *the* electronic device for each participant *and should be followed throughout the study. During the administration interview of the VinelandTM-II, MERS-R, and the CYBOCS-ASD audio recordings will be captured. These audio recordings will be reviewed by central clinicians to verify if these scales were administrated according to the rating standards. If necessary, raters will be contacted for remediation and additional training. It is not planned to extract any information about participant and caregiver from these audio recordings.*

[…]

Table 4 Overview Clinical Scales/Clinical Outcome Assessments

Scale group	Specific scale	Completed by	Children	Adolescents	Adults	Time [min]
SB5 abbrev. Stanford-Binet		clinician	mandatory	mandatory	mandatory	15-20
ADOS-2		clinician	mandatory	mandatory	mandatory	40-60
CGI-I+CGI-S		clinician	mandatory	mandatory	mandatory	5+5
CY-BOCS-ASD		clinician	mandatory	mandatory	mandatory	~ 20
MERS-R		clinician	mandatory	mandatory	mandatory	15-20

RBS-R		caregiver	mandatory	mandatory	mandatory	~ 15
RBQ-2 [1] ~~(at least one out of both)~~	RBQ-2 for Children	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	20-30
	RBQ-2A for adults	participant-reported	---	if deemed appropriate[1] by Investigator based on mental age.	mandatory	20-30
Routine Inventory[1] ~~(at least either CRI-R or ARI)~~	CRI-R for Children	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	~ 17
	ARI for adults	participant-reported	---	if deemed appropriate[1] by Investigator based on mental age	mandatory	~ 17
BRIEF	BRIEF for children	caregiver	mandatory	mandatory	---	10-15
	BRIEF-A for adults	caregiver	---	---	mandatory	10-15
Vineland™-II (survey)		clinician	mandatory	mandatory	mandatory	45-60
PedsQL	Family Impact Scale	caregiver	mandatory	mandatory	mandatory	~ 5
	Generic Core & Cognitive Functioning Scales	participant-reported	mandatory	mandatory	mandatory	~10

Table 4 Overview Clinical Scales/Clinical Outcome Assessments (cont.)

Scale group	Specific scale	Completed by	Children	Adolescents	Adults	Time [min]
SSP	Short Sensory profile	caregiver	mandatory	mandatory	-	5-15
Sleep[1]~~(at least either CSHQ or PSQI)~~	CSHQ	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	5-10
	PSQI	participant-reported	---	if deemed appropriate by Investigator[1]	mandatory	~ 5
RMET[2]	RMET-C for Children	participant-reported	if deemed appropriate[2] by Investigator	if deemed appropriate[2] by Investigator	if deemed appropriate[2] by Investigator	~ 20
	RMET-R for adults	participant-reported	---	if deemed appropriate[2] by Investigator	if deemed appropriate[2] by Investigator	~ 20
Anxiety[1]	HAM-A	clinician	---	---	mandatory	10-15
	PRAS-ASD	caregiver	mandatory	mandatory	---	~ 10
	BAI	participant-reported	---	if deemed appropriate[1] by Investigator	mandatory	5

1 *For scales where a pediatric and an adult scale or scale version exists, both versions should be administered in adolescents and adults, if deemed appropriate by Investigator. For further details, see protocol Section 8.1.1.3. In any case, at least one scale / scale version will be mandatory.*

2 *For the RMET, either the pediatric or adult version should be administered. If none of the two RMET versions is deemed appropriate for the participant the RMET can be skipped.*

8.1.1.1 Requirements for Caregivers

[…]

The caregiver arrangements for participants living in a residential home need to be assessed carefully on a case by case basis:

- *A staff member of the residential home can be the caregiver if this person spends sufficient time with the participant. In the opinion of the Investigator, the caregiver must be able to reliably assess the participant's mental status, activities, and behavior, and report on the participant's adherence and health. This would normally be possible when the caregiver spends a few hours each day with the participant.*

- *A family member living at the participant's home can be the caregiver if the participant returns home every night. When the participant returns home only over the weekend, a family member can only be the caregiver if they have intensive interaction with the participant during the week e.g., via phone calls, calls via Skype, SMS messages, etc. The quality of these interactions between caregiver and participant needs to be assessed for each participant to determine whether they are sufficient.*

- *A family member cannot be the caregiver when the participant lives full time in the residential home, unless the family member spends a few hours each day with the participant in the residential home.*

If in doubt about whether a participant's care arrangements are suitable for inclusion, the Investigator should discuss this with the Sponsor (Translational Medicine Leader or designee).

8.1.1.2 Administration of Participant-reported Scales to Illiterate Participants

For participants who are illiterate or have reading deficits the following procedure for the mandatory participant-reported scales should be used:

- *The scale administrator will read out the questions and answers and show the answers on the Rater station.*

- *The participant will choose one of the possible answers on the Rater station.*

- *If the participant is still unable to complete the scale even with the described assistance, the scale will be skipped. For adult participants only: where a similar caregiver-reported scale exists, that caregiver-reported scale will be completed instead of the skipped scale if it is deemed appropriate by Investigator (i.e., RBQ-2 if RBQ-2A is skipped, CRI-R if ARI is skipped, CSHQ if PSQI is skipped).*

8.1.1.3 Administration of both the Caregiver and Participant-reported Scale Version "if deemed appropriate by Investigator"

For adolescents and adults both versions of the Routine Inventories and the Repetitive Behavior Questionnaires scale should be administered in individual participants at the same visit if the Investigator deems the non-mandatory version of the scale appropriate (see Table 4 and Sections 8.1.1.10 and 8.1.1.11). This includes the participant-reported adult versions (RBQ-2A and ARI) and the caregiver-completed pediatric versions (RBQ-2 and CRI-R).

- *For adolescent participants the caregiver-completed RBQ-2 and CRI-R are mandatory scales. The participant-reported versions RBQ-2A and ARI will be completed as well, if deemed appropriate, and if the Investigator deems the participant able to complete these scales based on mental age.*

- *For adult participants the self-reported versions RBQ-2A and ARI are mandatory scales. The caregiver-reported RBQ-2 and CRI-R will be completed as well if deemed appropriate by Investigator.*

Similarly, and "if deemed appropriate by Investigator," the caregiver will complete the CSHQ for adult participants- Adolescent participants will complete the participant-reported PSQI and BAI (see Table 4).

If an adult participant is unable to complete a self-reported adult scale (e.g., because of mental age or other reasons) the corresponding caregiver-reported scale version will be used if it is deemed appropriate by Investigator and if such a scale version exists (i.e., RBQ-2 is to be completed if RBQ-2A is skipped, CRI-R if ARI is skipped, CSHQ if PSQI is skipped).

8.1.2.1 Drug Acceptability Survey

For the preparation of subsequent drug interventional studies and to optimize the formulation of study medications for these studies, caregivers *of children (age 5 to 12 years)* will be asked general questions about drug acceptability.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

[…]

After informed consent has been obtained, only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported (e.g., headache related to completion of the scales in this study) *until the participant has been discharged from the study.*

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after the participant has been discharged from the study.

However, if the Investigator learns of any SAE (including a death) or other adverse events of concern, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to *a protocol-mandated intervention,* ~~to study participation,~~ the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.4.1 Digital Biomarkers

[…]

For storage and analysis of audio recordings the Sponsor will follow, in detail, these guidelines: The raw audio data are encrypted in transfer and at rest (industry gold standard 256-bit asymmetric encryption). For data processing and analysis purposes, the raw audio data need to be decrypted. Decryption only occurs on a designated secure Roche server with tight access control. Access is granted to a named list of researchers only. Access will be limited to as few individuals as possible. The amount of raw audio data that is available in a decrypted format on this server is kept to an absolute minimum. To ensure this, decrypted data are either automatically re-encrypted or deleted immediately after being processed and analyzed. Analysis of the audio data is automated as far as is possible; manual listening to the raw audio data is kept to an absolute minimum. Manual listening will only be done in selected cases as a quality control step for the automated analysis process.

[…]

At the end of the study or at the time when the participant has completed the study, *both the* participants *and the caregivers* will be asked to complete satisfaction surveys on their experience using the smartphone during the study.

8.5.1 Screening Assessments

[…]

Screening assessments will be performed *during the* ~~at the~~ time *window* ~~points~~ indicated in the SoA (see Section 1.2), *i.e., within 4 to 2 weeks before the Baseline visit unless otherwise specified. However, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of caregivers or raters), the screening period may be extended to up to 6 weeks.*

At screening, t~~T~~ests~~, unless otherwise specified~~ for illicit drugs and alcohol misuse are at the Investigator's discretion. *The Investigator will decide if any tests are required or not to confirm eligibility in context of exclusion criterion #6. In addition, the selection of the appropriate tests and test parameters and the appropriate communication of possible findings to participant and parents according to local regulations will be at the discretion of the Investigator. Roche will support sites in the implementation process should the sites need (e.g., provision of urine dipsticks).*

Note: Any positive tests for amphetamines will need to be reviewed carefully by the Investigator on a case by case basis, because a significant proportion of people with ASD are taking stimulants such as methylphenidate for their attention-deficit problems. In such a case of a misleading drug alert, a possible study participant will not be excluded from the study.

9.1 SAMPLE SIZE JUSTIFICATION

[…]

- Age: children 5 to 12 years~~-old~~; adolescents 13 to 17 years~~-old~~ and adults 18 to 45 years~~-old~~

In addition, ~~15~~ *45 TD* healthy participants (*15* children *age* 5 to 12 years ~~of age~~, *15 adolescents age 13 to 17 years,* ~~old~~ *and 15 adults age 18 to 45 years* ~~old~~) will be enrolled for validation of *digital* biomarkers only.

9.2.1 Demographics and Baseline Characteristics

Summaries and listings will be prepared for all relevant Baseline characteristics such as IQ, age, sex, ADOS-2, ~~ADI-R,~~ VinelandTM-II, CY-BOCS-ASD, medical history including medications and treatments, caregiver status, educational status of participant and parents, etc.

9.2.5 Digital Biomarker Analyses

Digital biomarker data will be analyzed for: a) participant adherence; b) agreement between participant/caregiver reports and behavioral data; c) dependence on age and IQ and difference from *TD* healthy participants ~~(15 children)~~.

Appendix 1 Regulatory, Ethical, and Study Oversight Considerations

2.2. RETENTION OF RECORDS

[…]

~~If a~~*A*udio recordings ~~have been used, they~~ will be maintained on a secure server throughout the duration of the study and will be ~~destroyed one~~ *retained for at least 15* year*s* after study completion ~~on approval by the Sponsor~~. *No records may be destroyed during the retention period without the written approval of the Sponsor.*

Appendix 2: Adverse Events: Definitions and Procedures for Evaluating, Follow up and Reporting

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event~~, regardless of relationship to study mandated procedures~~:

- Serious adverse events *caused by a protocol-mandated intervention only.*

[…]

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS

[…]

For reports of serious adverse events caused by a protocol-mandated intervention that occur after the Baseline visit, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to

the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event is believed to be related to protocol-mandated intervention the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABIQ	Abbreviated Battery Intelligence Quotient
ADOS	Autism Diagnostic Observational Schedule
ABA	*Applied behavioral analysis*
AE	Adverse event
APP	Application on smartphone
ARI	Adult Routines Inventory
ASD	Autism Spectrum Disorder
BRIEF	Behaviour Rating Inventory of Executive Function
CGI-I	Clinical Global Impression-improvement
CGI-S	Clinical Global Impression-severity
CNS	Central nervous system
COA	Clinical outcome assessments
CRI-R	Childhood Routines Inventory- Revised
CRO	Contract research organization
CSAP	Clinical statistical analysis plan
CSHQ	Child's Sleep Habits Questionnaire Sleep Diary
CSR	Clinical study report
CTD	Common technical document
CY-BOCS-ASD	Children's Yale-Brown Obsessive Compulsive Scale modified for Autism Spectrum Disorder
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eCOA	Electronic clinical outcome assessment
ESF	Eligibility screening form
FSIQ	Full Scale Intelligence Quotient
ICC	Intra class correlations
ICH	International *Council for* Harmonisation
IMP	Investigational medicinal product
IQ	Intelligence quotient
IRB	Institutional Review Board
IRF	Independent review facility
IRC	Independent Review Committee
IS	Insistence of sameness

Abbreviation	Definition
LPLV	Last participant, last visit
LPLO	Last participant, last observation
MERS	Montefiore Einstein Rigidity Scale
NOAEL	No-observed-adverse-effect level
NSAESI	Non-serious adverse event of special interest
ObsRO	Observer-reported outcome
OTC	Over-the-counter
PedsQL	Pediatric Quality of Life Inventory
PD	Pharmacodynamic
PSQI	Pittsburg Sleep Quality Index
RBQ-2	Restricted Behavior Questionnaire
RBS-R	Repetitive Behavior Scale-Revised
RMET	*Reading the Mind in the Eyes Test*
RRB	Restricted and repetitive behavior
RSMB	Repetitive sensory and motor behaviors
SAE	Serious adverse event
SD	Single dose
SoA	Schedule of activities
SOP	Standard operating procedure
SB	Stanford-Binet intelligence scales
TD	*Typically developing*

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**STUDY TO EVALUATE AND EXPLORE SCALES FOR REPETITIVE AND RESTRICTED BEHAVIORS AND DIGITAL BIOMARKERS IN CHILDREN, ADOLESCENTS AND ADULTS WITH AUTISM SPECTRUM DISORDER (ASD)**
SHORT TITLE	**Evaluation of scales for repetitive and restricted behaviors, digital biomarkers in children, adolescents and adults with ASD**
PROTOCOL NUMBER:	BP40331
VERSION:	2
TEST PRODUCT:	NA
PHASE:	I

RATIONALE

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social communication and social interaction and presence of repetitive patterns of behaviors, interests, or activities. In addition to these core deficits, individuals with ASD may suffer from a range of co-morbid conditions and associated behavioral problems, including irritability, depression or anxiety, attention deficits, obsessive compulsive symptoms, seizures and sleep disruption. Restricted and repetitive behaviors (RRBs) are core diagnostic features of ASD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The prevalence of ASD is between 1 in 45 to 1 in 68 children. The etiology of ASD is highly genetic although environmental factors also contribute. Heritability estimates from family and twin studies suggest that about 90% of variance can be attributed to genetic factors, making ASD the neuropsychiatric disorder most affected by genetic factors. At present, no pharmacological treatment has been approved by Health Authorities to treat the core deficits of ASD, and currently available approved drugs in the US only (risperidone and aripiprazole) address only associated behavioral problems (used for the treatment of irritability associated with ASD). Non-pharmacological treatments have been developed to address the core symptoms; however, clear efficacy has been difficult to demonstrate in large controlled clinical trials and they are time consuming and costly. Accordingly, there is a high unmet medical need for pharmacological treatments of these core symptoms of the disorder.

RRBs constitute a broad range of behaviors, including simple motor stereotypies as well as more complex ritualized and rigid behaviors, compulsions, and restricted interests that vary in frequency, intensity, and duration. Although there is an extensive literature on RRBs in subjects with ASD, the instruments available and widely used to assess these behaviors in clinical trials are not fully understood or have limitations to assess change in these behaviors, in particular in clinical trials. BP40331 is a non-drug study which seeks to characterize different scales to measure repetitive and restricted behaviors in different ASD sub-populations over time and also to explore the use of digital biomarkers. The results from this study will inform the planning and setup of subsequent drug interventional studies in programs aimed to treating restrictive and repetitive behaviors in ASD.

OBJECTIVES AND ENDPOINTS

Primary Objectives	
• To characterize and compare the psychometric properties of different scales for RRB in individuals with ASD.	
Secondary Objectives	
• To evaluate the effect of Age and intelligence quotient (IQ) on RRB in participants with ASD. • To evaluate correlations between scales. • To explore the factor structure within each scale.	
Tertiary/Exploratory Objectives	**Endpoints**
• To assess participant adherence to remote monitoring with a smartphone application and wearable.	• Days on which participants collect data using the smartphone and wearable.
• To capture daily participant and/or caregiver reports of core ASD symptoms with smartphone application (app).	• Daily participant/caregiver-reported outcome ratings of RRBs and social interaction.
• To continuously and objectively measure ASD symptoms with wearable technology.	• Frequency of repetitive movements. • Frequency of locations visited around the home and beyond. • Relationship between anxiety and heart rate.
• To frequently measure social and cognitive performance with smartphone app.	• Accuracy and speed of emotion recognition. • Spatial working memory capacity. • Speech properties (pitch, volume, shimmer, jitter). • Conversational patterns (duration of speech, turn-taking).

OVERALL DESIGN

Each participant with ASD will be evaluated using several scales and tests at each visit at the clinic. There will be four clinic visits in total (screening period included). Table 1 provides an overview of scales and tests to be used in the study. In addition, digital biomarker data will be collected from all participants. *Typically developing (TD)* healthy participants will be enrolled for validation of digital biomarkers only.

Table 4 Overview Clinical Scales/Clinical Outcome Assessments

Scale group	Specific scale	Completed by	Children	Adolescents	Adults	Time [min]
SB5 abbrev. Stanford-Binet		clinician	mandatory	mandatory	mandatory	15-20
ADOS-2		clinician	mandatory	mandatory	mandatory	40-60
CGI-I+CGI-S		clinician	mandatory	mandatory	mandatory	5+5
CY-BOCS-ASD		clinician	mandatory	mandatory	mandatory	~ 20
MERS-R		clinician	mandatory	mandatory	mandatory	15-20
RBS-R		caregiver	mandatory	mandatory	mandatory	~ 15
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	RBQ-2A for adults	participant-reported	---	if deemed appropriate[1] by Investigator based on mental age	mandatory	20-30
Routine Inventory[1]	CRI-R for Children	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	~ 17
	ARI for adults	participant-reported	---	if deemed appropriate[1] by Investigator based on mental age	mandatory	~ 17
BRIEF	BRIEF for Children	caregiver	mandatory	mandatory	---	10-15
	BRIEF-A for Adults	caregiver	---	---	mandatory	10-15
Vineland™-II (survey)		clinician	mandatory	mandatory	mandatory	45-60
PedsQL	Family Impact Scale	caregiver	mandatory	mandatory	mandatory	~ 5
	Generic Core & Cognitive Functioning Scales	participant-reported	mandatory	mandatory	mandatory	~10

Table 4 Overview Clinical Scales/Clinical Outcome Assessments (cont.)

SSP	Short Sensory profile	caregiver	mandatory	mandatory	-	5-15
Sleep[1]	CSHQ	caregiver	mandatory	mandatory	if deemed appropriate [1] by Investigator	5-10
	PSQI	participant-reported	---	if deemed appropriate[1] by Investigator	mandatory	~ 5
RMET[2]	RMET-C for Children	participant-reported	if deemed appropriate [2] by Investigator .	if deemed appropriate[2] by Investigator.	if deemed appropriate [2)] by Investigator	~ 20
	RMET-R for adults	participant-reported	---	if deemed appropriate[2] by Investigator.	if deemed appropriate [2] by Investigator	~ 20
Anxiety[1]	HAM-A	clinician	---	---	mandatory	10-15
	PRAS-ASD	caregiver	mandatory	mandatory	---	~ 10
	BAI	participant-reported	---	if deemed appropriate[1] by Investigator	mandatory	5

1. *For scales where a pediatric and an adult scale or scale version exists, both versions should be administered in adolescents and adults, if deemed appropriate by Investigator. For further details see protocol Section 8.1.1.3. In any case at least one scale / scale version will be mandatory.*
2. *For the RMET, either the pediatric or adult version should be administered. If none of the two RMET versions is deemed appropriate for the participant the RMET can be skipped.*

Length of Study

The total duration of the study (from screening through to study completion) for each participant will be approximately 15 weeks divided as follows:

- Screening and run-in period: up to 4 weeks.
- Study period: 12 weeks.

End of Study

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 12 weeks after the last participant had the Baseline visit.

PARTICIPANT POPULATION

The participants are children *age* 5 to 12 years, adolescents *age* 13 to 17 years, and adults *age* 18 to 45 *years* who meet all diagnostic criteria of ASD according to the DSM-5 criteria.

In addition, *45 TD* healthy participants (*15* children age 5 to 12 years, *15 adolescents age 13 to 17 years, and 15 adults age 18 to 45 years*) will be enrolled for validation of digital biomarkers only.

INCLUSION/EXCLUSION CRITERIA

INCLUSION CRITERIA

Participants with ASD and *TD* healthy participants are eligible to be included in the study only if all of the following criteria apply:

Inclusion criteria specific to *typically developing* healthy participants:

1. Male and female *TD* healthy participants age 5 to *45* years inclusive.

Inclusion criteria specific to *typically developing* healthy participants and participants with ASD:

2. Able and willing to provide written informed consent or assent, as per local requirements according to International Council for Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the participant according to ICH and local regulations and assent must be given whenever possible.
3. Availability of a parent or other reliable caregiver who is fluent in English and has frequent and sufficient contact with the participant. The same person must agree to accompany the participant to all clinic visits and provide information about the participant's behavior and symptoms and must agree to oversee the participant's adherence with protocol-specified procedures.
4. In the Investigator's opinion, the participant must be able to participate and is deemed appropriate for participation in the study, capable of following the study schedule of assessments.
5. *English proficiency compatible with the study measurements as judged by the Investigator.*
6. Hearing, vision, *and speech* compatible with the study measurements as judged by the Investigator.

Inclusion criteria specific to participants with ASD:

7. Male and female participants with ASD 5 to 45 years inclusive.
8. Abbreviated Battery Intelligence Quotient (ABIQ) ≥ 50 as assessed by Stanford-Binet Intelligence Scales fifth Edition (SB5) at screening or within the last 12 months prior to screening.
9. ASD diagnosis by DSM-5 criteria by a qualified clinician.
10. The ASD diagnosis confirmed by Autism Diagnostic Observation Schedule (ADOS-2) done by a certified rater at screening, or within the last 6 months prior to screening.
11. Children's Yale-Brown Obsessive Compulsive Scale modified for ASD (CY-BOCS-ASD) total score of at least 12.
12. Clinical Global Impression–Severity (CGI-S) scale ≥ 4 (moderately ill) at screening about participant's current autism severity.
13. Medications should be stable for 4 weeks (6 weeks for Fluoxetine) and behavioral interventions for 6 weeks prior to screening. Investigator expects stability of these treatments for the duration of the study.

EXCLUSION CRITERIA

Participants with ASD and *TD* healthy participants are excluded from the study if any of the following criteria apply:

Exclusion criteria specific to *typically developing* healthy participants:

1. *Typically developing* healthy *participants* with first degree relative with ASD.

Exclusion criteria specific to *typically developing* healthy participants and participants with ASD:

2. Participation in an investigational drug or device study within 4 weeks, or five times the half-life (if it is a drug study) of the investigational molecule (whichever is longer), prior to screening and the participant is expected not to enroll in any other trial during the study.
3. Co-occurring disease or condition that could interfere with, or treatment which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.
4. Unstable or uncontrolled clinically significant psychiatric and/ or neurological disorder that may interfere with the objectives of the study.

Exclusion criteria specific to participants with ASD:

5. Participants with known "syndromic" ASD (e.g., Fragile-X syndrome, Angelman Syndrome, Prader-Willi, Rett's syndrome, tuberous sclerosis, Dup15q syndrome).
6. History of alcohol misuse and/or illicit drug use during the last 12 months *prior to screening*.

NUMBER OF PARTICIPANTS

Approximately 90 participants with ASD will be enrolled into six cohorts with approximately 15 participants each. The six cohorts are defined by all combinations of the below categories for the two factors ABIQ and age:

- ABIQ: participants with ABIQ $\geq$ 70 vs participants with ABIQ $\geq$ 50 and $<$ 70.
- Age: children 5 to 12 years; adolescents 13 to 17 years and adults 18 to 45 years.

In addition, *45 TD* healthy participants (*15* children age 5 to 12 years, *15 adolescents age 13 to 17 years, and 15 adults age 18 to 45 years*) will be enrolled for validation of *digital* biomarkers only.

CONCOMITANT MEDICATIONS

Any stable medication (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) at screening should remain stable throughout the study. However, dose changes due to adjustments for change in body weight/ age and or triggered by therapeutic monitoring will be allowed. Other changes in prescribed medication need to be approved by the Sponsor (Medical Monitor or designee).

Non-Pharmacological Interventions

Non-pharmacological interventions (e.g., subject psychotherapy, cognitive behavioral therapy, applied behavioral analysis (ABA), speech therapy, occupational therapy, rehabilitative therapy, and social skills training) must be stable for 4 weeks prior to screening and must remain stable throughout the ongoing study in terms of type of intervention and intensity. Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to school holidays; changes in college/school programs) are not considered significant and need not to be discussed with the Sponsor (Medical Monitor or designee).

A complete history of non-pharmacological interventions for the treatment of ASD including all previously completed therapies will be reported on eCRF.

1.2 SCHEDULE OF ACTIVITIES

The schedule of the activities is provided in Table 1 and Table 2.

Table 1 Schedule of Activities – Main table (ASD participants only)

	Screening Clinic visit [1]	Baseline Clinic visit [1]	Week 2 Clinic visit [1]	Week 5 Phone [3] Contact	Week 8 Phone [3] Contact	Week 12 Clinic visit [1]	Early With-drawal Clinic visit [1]
Day	**-21**	**1**	**15**	**36**	**57**	**85**	**NA**
Time window (days)	**+/- 7**	**NA**	**+/-2**	**+/-4**	**+/-4**	**+/-7**	**NA**
Informed Consent	X						
Stanford Binet (SB-5) abbreviated IQ test [4]	X						
ADOS-2 [5]	X						
CY-BOCS-ASD	X	X	X			X	X
CGI-S	X	X	X			X	X
CGI-I			X			X	X
Incl/Excl criteria	X						
Demography	X						
Medical History (incl. psychiatry)	X						
MERS-R		X	X			X	X
RBS-R		X	X			X	X
RBQ-2 [6]		X	X			X	X
CRI-R [6] / ARI [6]		X	X			X	X
BRIEF		X	X			X	X
Vineland™-II (survey)		X				X	X
PedsQL (family impact scale)		X	X			X	X
PedsQL (core and cognitive scale)		X	X			X	X
SSP		X	X			X	X
CSHQ [6] / PSQI [6]		X	X			X	X
HAM-A [6] / BAI [6] / PRAS-ASD [6]		X	X			X	X
RMET [6]		X				X	X
Drug Acceptability Survey			X				
Phone contacts [3]				X	X		
Previous & Concomitant Treatments	←	—	—	—	—	—	→
Adverse Events [7]	←	—	—	—	—	—	→
Digital Biomarkers [2]	←	—	—	—	—	—	→

1. Clinical visits can be performed over 2 days.
2. See Table 2 for collection of Digital Biomarker data from all participants.
3. Follow-up by telephone will include questions about participant's welfare.
4. A Stanford-Binet Intelligence scales test up to 12 month old is acceptable.
5. An ADOS-2 test up to 6 month old is acceptable.
6. Age specific scales, and scales deemed appropriate by Investigator, will be completed for details (see Table 4).
7. Only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported (see Section 8.3).

Table 2 Schedule of Activities for Collection of Digital Biomarkers. All participants (*typically developing* healthy participants and participants with ASD)

	Screening Clinic visit [1]	Baseline Clinic visit [1]	Week 2 Clinic visit [1] Or [6] Phone Contact [3]	Week 5 Phone [3] Contact	Week 8 Phone [3] Contact	Week 12 Clinic visit [1]	Early With-drawal Clinic visit [1]
Day	-21	1	15	36	57	85	NA
Time window (days)	+/- 7	NA	+/-2	+/-4	+/-4	+/-7	NA
Informed Consent	X						
Stanford Binet (SB-5) abbreviated IQ test [2]	X						
Incl/Excl criteria	X						
Demography	X						
Identification of targeted behaviors for app	X						
Hand over devices and training	X						
dBM run-in to validate devices and apps	←	→					
RMET [4]		X				X	X
Digital Biomarker Collection		←	—	—	—	—	→
Phone contacts [3]			X [8]	X	X		
Return devices and satisfaction survey [5]						X	X
Adverse Events [7]	←	—	—	—	—	—	→

Digital biomarkers will be collected from all participants, those with ASD and the *typically developing (TD)* healthy participants.

1. Clinical visits can be performed over 2 days.
2. A Stanford-Binet Intelligence scales test up to 12 month old is acceptable.
3. Follow-up by telephone will include questions about participant's welfare and progress in collection of digital biomarker data.
4. The RMET will provide anchor data for analysis of digital biomarkers and will be conducted also in *TD* healthy participants. An age specific version of the RMET will be completed as deemed appropriate by Investigator for details (see Table 4).
5. Final satisfaction surveys on the participant's experience about collection of digital biomarker will be completed by participants *and by caregivers*.
6. For all participants with ASD at week 2 a mandatory clinic visit will be completed. For the *TD* healthy participants at week 2 a telephone contact will be sufficient.
7. Only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported see Section 8.3.

2. INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent deficits in social communication and social interaction and presence of repetitive patterns of behaviors, interests, or activities. The prevalence of ASD is between 1 in 45 to 1 in 68 children (Zablotsky et al 2015, Christensen et al 2016, Blumberg et al 2013). Core symptoms of ASD are usually observed by 3 years of age, although language development might delay identification of symptoms. Moreover, although initial symptoms may be identified between 12 and 24 months, typically this does not manifest as a formal diagnosis and even if a diagnosis is made, this may not be stable (Kleinman et al 2008; Chawarska et al 2009). Deficits in social interaction manifest themselves as impaired use of nonverbal communication, delayed and reduced interactions with peers, absent sharing of enjoyable experiences and interest with peers, and lack of social judgment. Abnormalities in communication may include a delay in verbal language development, impaired expressive language, deficient language pragmatics, as well as stereotyped, repetitive, or idiosyncratic use of language. Stereotyped and repetitive behavior manifests as a preoccupation with stereotyped or restricted interests, adherence to routines, rigidity, perseveration, motor mannerisms, and preoccupation or fascination with parts of items and unusual visual exploration. In addition to these core deficits, individuals with ASD may suffer from a range of co-morbid conditions and associated behavioral problems, including irritability, depression or anxiety, attention deficits, obsessive compulsive symptoms, seizures and sleep disruption (Houghton et al 2017). The etiology of ASD is highly genetic although environmental factors also contribute. Heritability estimates from family and twin studies suggest that about 90% of variance can be attributed to genetic factors, making ASD the neuropsychiatric disorder most affected by genetic factors (Levy et al 2009).

At present, no pharmacological treatment has been approved by Health Authorities to treat the core deficits of ASD, and currently available approved drugs in the US only (risperidone and aripiprazole) address only associated behavioral problems (used for the treatment of irritability associated with ASD) (Wink et al 2010). Non-pharmacological treatments have been developed to address the core symptoms; however, clear efficacy has been difficult to demonstrate in large controlled clinical trials and they are time consuming and costly (Warren et al 2011). Accordingly, there is a high unmet medical need for pharmacological treatments of these core symptoms of the disorder.

2.1 STUDY RATIONALE

Restricted and repetitive behaviors (RRBs) are core diagnostic features of ASD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). RRBs constitute a broad range of behaviors, including simple motor stereotypies as well as more complex ritualized and rigid behaviors, compulsions, and restricted interests that vary in frequency, intensity, and duration.

Factor analysis of RRBs have identified at least two groups of RRBs; one comprising repetitive sensory and motor behaviors (RSMB) also known as lower-order RRBs such as hand flapping and body rocking, and the other comprising more abstract behaviors also called insistence on sameness (IS) or “higher-order” RRBs, such as routines and circumscribed interests (Richler et al 2010). Although there is an extensive literature on RRBs in subjects with ASD, the instruments available and widely used to assess these behaviors in clinical trials are not fully understood or have limitations to assess change in these behaviors, in particular in clinical trials (Scahill et al 2015).

BP40331 is a non-drug study which seeks to characterize different scales to measure repetitive and restricted behaviors in different ASD sub-populations over time and also to explore the use of digital biomarkers. The results from this study will inform the planning and setup of subsequent drug interventional studies in programs aimed to treating restrictive and repetitive behaviors in ASD.

2.2 BENEFIT/RISK ASSESSMENT

Participants are not expected to experience physical, psychological or social harm by participating in study BP40331. As no study treatment will be given and no invasive procedures will be performed in this study there are no risks associated with participation in this study. Digital biomarkers assessments using smartphone and other sensors are not expected to cause harm or major inconvenience to the participants.

There is no individual benefit for ASD participants in this study. However, the results of this study may help the evaluation in future Phase II studies in subjects with ASD, ensuring that the most optimal scales and tests will be used to demonstrate efficacy of new drugs to treat restrictive and repetitive behaviors in ASD. Data are not considered to be detrimental for caregivers and participants and individual results will be shared at the end of the study, if requested.

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 3.

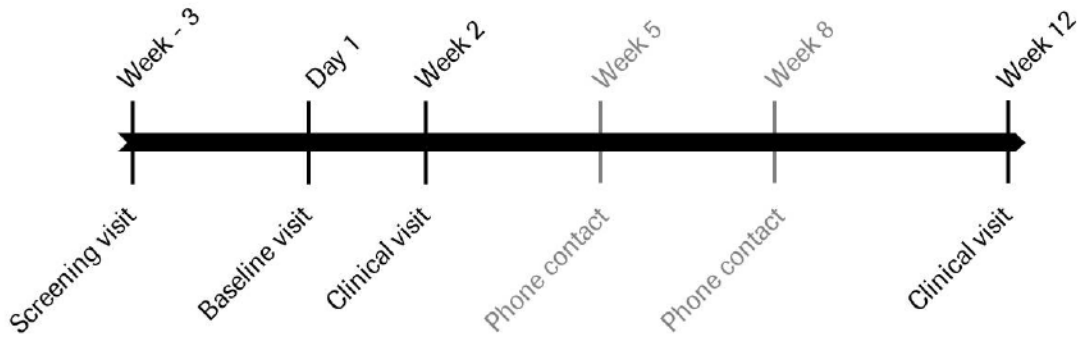
Table 3 Objectives and Endpoints

Primary Objectives	
• To characterize and compare the psychometric properties of different scales for RRB in individuals with ASD.	
Secondary Objectives	
• To evaluate the effect of age and intelligence quotient (IQ) on RRB in participants with ASD. • To evaluate correlations between scales. • To explore the factor structure within each scale.	
Tertiary/Exploratory Objectives	**Endpoints**
• To assess participant adherence to remote monitoring with a smartphone application and wearable.	• Days on which participants collect data using the smartphone and wearable.
• To capture daily participant and/or caregiver reports of core ASD symptoms with smartphone application (app).	• Daily participant/caregiver-reported outcome ratings of RRBs and social interaction.
• To continuously and objectively measure ASD symptoms with wearable technology.	• Frequency of repetitive movements. • Frequency of locations visited around the home and beyond. • Relationship between anxiety and heart rate.
• To frequently measure social and cognitive performance with smartphone app.	• Accuracy and speed of emotion recognition. • Spatial working memory capacity. • Speech properties (pitch, volume, shimmer, jitter). • Conversational patterns (duration of speech, turn-taking).

3.1 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

Figure 1 Overview of Study Design



4. STUDY DESIGN

4.1 OVERALL DESIGN

An overview of the study design is provided in Section 3.1.

Each participant with ASD will be evaluated using several scales and tests at each visit at the clinic. A total of four clinic visits and two phone contacts are planned (screening period included; see Table 1). In addition, digital biomarker data will be collected from all participants. *Typically developing (TD)* healthy participants will be enrolled for validation of *digital* biomarkers only, see Table 2.

4.1.1 Length of the Study

The total duration of the study (from screening through to study completion) for each participant will be approximately 15 weeks divided as follows:

- Screening and run-in period: up to 4 weeks. *However, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of caregivers or raters), the screening period may be extended to up to 6 weeks.*
- Study period: 12 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

In contrast to an extensive literature on RRBs in subjects with ASD there are considerable gaps in the knowledge about the available and widely used scales (e.g., Repetitive Behavior Scale-Revised [RBS-R]) to assess these behaviors, particularly in clinical trials.

The overall study design with four planned clinic visits including a screening visit and a week 12 visit (see Section 1.2) aims to mimic the design of a drug interventional study over 12 weeks and will help to evaluate the performance of these scales under conditions comparable with interventional studies over 12 weeks. A second administration of all RRB scales 2 weeks after the Baseline visit was judged as

appropriate to assess test-re-test reliability. These visits are also appropriate to estimate internal consistency, stability, variability, minimal clinically important differences of included scales.

The study rationale is provided in Section 2.1.

4.2.1 Rationale for Study Population

Children, adolescents and adults (aged 5-45 years) with clinical diagnosis of ASD according to DSM-5 criteria and confirmed by Autism Diagnostic Observational Schedule (ADOS-2) will be enrolled. The lower age limit (5 years) will allow building a significant database from broad pediatric population. Although data suggest that the diagnosis of ASD is possible below the age of 5, the diagnosis is less reliable and may not be stable, and as a consequence will be excluded from this trials, although younger participants may be included in future trials.

Participants with at least moderate ASD symptoms and current presence of RRBs will be recruited to allow the monitoring of these behaviors during the study. To this aim, only participants with a Clinical Global Impression-severity (CGI-S) $\geq$ 4 (at least moderately-ill) and a Children's Yale-Brown Obsessive Compulsive Scale in Autism Spectrum Disorder (CY-BOCS-ASD) total score of at least 12 at screening will be enrolled. Participants with a low intelligence quotient (IQ) below 50 (Stanford-Binet Intelligence Scales 5th edition Abbreviated Battery Intelligence Quotient scale (ABIQ) will be excluded because of the higher prevalence of significant co-morbidities in this population.

Since there is wide consensus that the nature and intensity of RRBs depend on age and IQ, participants will be recruited into six cohorts of 15 participants to ensure enough variance across these two factors. Cohorts will be stratified firstly on ABIQ (participants who have an ABIQ $\geq$ 70 versus participants who have an ABIQ $\geq$ 50 and $<$ 70), and secondly based on age (children, adolescents and adults; see Section 5).

4.2.2 Rationale for Control Group

This study includes a group of *TD* healthy male and female *participants (15 children* age 5 to 12 years*, 15 adolescents age 13 to 17 years, and 15 adults age 18 to 45 years*). The *TD* healthy participants will be needed to compare and validate the digital biomarkers versus participants with ASD. The *TD* healthy control group will participate in collection of digital biomarker data (see *Schedule of Activities [*SoA*]* for digital biomarkers, Table 2) and except of the *Reading the Mind in the Eyes Test (*RMET*)* needed as anchor data for the analysis of digital biomarkers, no clinical scales will be performed in the *TD* healthy control group since these scales are not suitable for typically developed individuals (see main SoA, Table 1).

4.2.3 Rationale for Biomarker Assessments

There are several limitations of the current clinical assessments performed during clinical visits including: (1) severity of a participant's symptoms may vary from day-to-day;

(2) the episodic nature of symptoms mean that the symptom may not occur during the clinical visit; (3) effects can be masked at clinic visits by a variety of factors, including the "White-Coat Effect" where participants try harder at performance outcome measures when a doctor is present; (4) the subjectivity of participant or caregiver evaluation of symptom severity; and (5) the assessments are done in a non-naturalistic environment.

Digital biomarkers have the potential to address these issues by providing frequent and objective measurements in the participant's normal environment. Digital biomarkers are defined here as physiological and behavioral data collected with consumer electronics for the purpose of tracking health-related outcomes. A digital biomarker approach has been developed for this study where participants will be tracked with a combination of: (1) daily participant and caregiver-reported outcome measures ('surveys'), (2) daily performance outcome measures ('active tests') and (3) continuous passive monitoring of participant behavior.

A dedicated smartphone and wearable device will be provided to each participant and caregiver. The active tests and surveys contained in the smartphone app will provide regular daily recording of disease signs, enabling the characterization of progression over time. Analysis of the data will aim to identify the occurrence of repetitive movements, understand patterns of movement around the home and beyond, the stereotype of sensor signals across days as a proxy for ritualistic behavior, changes in heart rate associated with anxiety, and aspects of social functioning. This data will provide continuous objective quantification of these variables throughout the study.

4.3 END OF STUDY DEFINITION

The end of the study is defined as the date when the last participant last observation (LPLO) occurs. LPLO is expected to occur approximately 12 weeks after the last participant had his/her Baseline visit.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants are children *age* 5 *to* 12 years, adolescents *age* 13 *to* 17 years, and adults *age* 18 *to* 45 *years* who meet all diagnostic criteria of ASD according to the DSM-5 criteria (see Section 5.1).

Approximately 90 participants with ASD will be enrolled into six cohorts with approximately 15 participants each by two factors ABIQ and age:

- ABIQ: participants with ABIQ $\geq$ 70 vs participants with (ABIQ $\geq$ 50 and $<$ 70)
- Age: children 5 *to* 12 years; adolescents 13 *to* 17 years and adults 18 *to* 45 years

In addition, 45 TD healthy participants (15 children age 5 to 12 years, 15 adolescents age 13 to 17 years, and 15 adults age 18 to 45 years) will be enrolled for validation of digital biomarkers only. See Section 9.1 (sample size justification) for further details.

Prospective approval of protocol deviations from recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants with ASD and TD healthy participants are eligible to be included in the study only if all of the following criteria apply:

Inclusion criteria specific to *typically developing* healthy participants:

1. Male and female TD healthy participants age 5 to 45 years inclusive.

Inclusion criteria specific to *typically developing* healthy participants and participants with ASD:

2. Able and willing to provide written informed consent or assent, as per local requirements according to International Council for Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the participant according to ICH and local regulations and assent must be given whenever possible.
3. Availability of a parent or other reliable caregiver who is fluent in English and has frequent and sufficient contact with the participant (see Section 8.1.1.1). The same person must agree to accompany the participant to all clinic visits and provide information about the participant's behavior and symptoms and must agree to oversee the participant's adherence with protocol-specified procedures.
4. In the Investigator's opinion, the participant must be able to participate and is deemed appropriate for participation in the study, capable of following the study schedule of assessments.
5. *English proficiency compatible with the study measurements as judged by the Investigator.*
6. Hearing, vision, *and speech* compatible with the study measurements as judged by the Investigator.

Inclusion criteria specific to participants with ASD:

7. Male and female participants with ASD 5 to 45 years inclusive.
8. Abbreviated Intelligence Battery Quotient (ABIQ) $\geq$ 50 as assessed by Stanford-Binet Intelligence Scales fifth Edition (SB5) at screening or within the last 12 months prior to screening.
9. ASD diagnosis by DSM-5 criteria by a qualified clinician.
10. The ASD diagnosis confirmed by ADOS-2 done by a certified rater at screening or within the last 6 months prior to screening.

11. Children's Yale-Brown Obsessive Compulsive Scale modified for ASD (CY-BOCS-ASD) total score of at least 12.
12. Clinical Global Impression–Severity (CGI-S) scale ≥ 4 (moderately ill) at screening about participant's current autism severity (see Section 8.1.1.7).
13. Medications should be stable for 4 weeks (6 weeks for Fluoxetine) and behavioral interventions for 6 weeks prior to screening. Investigator expects stability of these treatments for the duration of the study.

5.2 EXCLUSION CRITERIA

Participants with ASD and *TD* healthy participants are excluded from the study if any of the following criteria apply:

Exclusion criteria specific to *typically developing* healthy participants:

1. *Typically developing* healthy *participants* with first degree relative with ASD.

Exclusion criteria specific to *typically developing* healthy participants and participants with ASD:

2. Participation in an investigational drug or device study within 4 weeks, or five times the half-life (if it is a drug study) of the investigational molecule (whichever is longer), prior to screening and the participant is expected not to enroll in any other trial during the study.
3. Co-occurring disease or condition that could interfere with, or treatment which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the participant in this study.
4. Unstable or uncontrolled clinically significant psychiatric and/ or neurological disorder that may interfere with the objectives of the study.

Exclusion criteria specific to participants with ASD:

5. Participants with known "syndromic" ASD (e.g., Fragile-X syndrome, Angelman Syndrome, Prader-Willi, Rett's syndrome, tuberous sclerosis, Dup15q syndrome).
6. History of alcohol misuse and/ or illicit drug use during the last 12 months *prior to screening*.

5.3 LIFESTYLE CONSIDERATIONS

No lifestyle restrictions required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Screen-failed participants can be re-screened with Sponsor permission (Medical Monitor or designee) if there is a substantial change in the participant's general condition (e.g., a new medication should have been stable for at least 4 weeks at re-screening) and if recruitment for the study is still ongoing. Re-screening of participants with ASD will not be allowed if the participant failed earlier to meet the disease-specific inclusion criteria (CYBOCS-ASD, ADOS-2, CGI-S, and ABIQ).

Screening assessments will be performed during the time window indicated in the SoA (see Section 1.2), i.e., within 4 to 2 weeks before the Baseline visit. However, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of caregivers or raters), the screening period may be extended to up to 6 weeks. Beyond 6 weeks the participant is considered a screen failure, but can be re-screened.

5.5 RECRUITMENT PROCEDURES (*TYPICALLY DEVELOPING* HEALTHY PARTICIPANTS)

Participants will be identified for potential recruitment using pre-screening enrollment logs, clinical database and IEC/IRB approved advertisements prior to consenting to take place on this study.

6. TREATMENTS

This is a non-drug study and therefore no study treatment (IMP or non-IMP) will be administered.

6.1 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There will be no randomization and no blinding

6.2 CONCOMITANT THERAPY

For participants with ASD any stable prescribed medication at screening should remain stable throughout the study. However, dose changes due to adjustments for change in body weight/ age and or triggered by therapeutic monitoring will be allowed. Other changes in prescribed medication need to be approved by the Sponsor (Medical Monitor or designee).

For *TD* healthy participants as a general rule, no concomitant therapies will be permitted, with the exception of medications to treat adverse events. However, approval for concomitant therapies can be obtained on case by case basis after discussion between the Investigator and the Sponsor (Medical Monitor or designee). The case needs to be clearly documented.

6.2.1 Permitted Therapy for Participants with ASD

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) used by a participant

from *12* weeks prior to screening until the follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency). Details of psychosocial/non-pharmacological interventions used over the past year are to be documented in detail see section 6.2.2.

The Sponsor (Medical Monitor or designee) should be contacted if there are any questions regarding concomitant or prior therapy. All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). All therapy and/or medication administered to manage adverse events should be recorded on eCRF.

6.2.2 Non-Pharmacological Interventions for Participants with ASD

Non-pharmacological interventions (e.g., subject psychotherapy, cognitive behavioral therapy, applied behavioral analysis [ABA], speech therapy, occupational therapy, rehabilitative therapy, and social skills training) must be stable for *6* weeks prior to screening and must remain stable throughout the ongoing study in terms of type of intervention and intensity. Minor changes in ongoing treatment (e.g., missed therapy sessions due to holiday/vacation; planned break in therapy due to school holidays; changes in college/school programs) are not considered significant and need not to be discussed with the Sponsor (Medical Monitor or designee).

A complete history of non-pharmacological interventions for the treatment of ASD including all previously completed therapies will be reported on eCRF and will include start and end date, name of therapy and number of hours per week.

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL

An excessive rate of withdrawals can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1.

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

Only participants who withdraw from the study before completion of the week 2 visit will be replaced (in the same cohort).

See SoA (Section 1.2) for data to be collected at the time of early withdrawal visit.

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their time-points are summarized in the Schedules of Activities (SoA; Section 1.2). Protocol waivers or exemptions are not allowed.

8.1 EFFICACY ASSESSMENTS

8.1.1 Clinical Outcome Assessments

Caregivers, clinicians and participants will use an electronic device to capture clinical outcome assessments (COA) specified below (see Appendix 1; 2.1.2.1.). The sequence of assessments *specific for each age cohort is* pre-defined on *the* electronic device for each participant *and should be followed throughout the study. During the administration interview of the Vineland™-II, MERS-R, and the CYBOCS-ASD audio recordings will be captured. These audio recordings will be reviewed by central clinicians to verify if these scales were administrated*

according to the rating standards. If necessary, raters will be contacted for remediation and additional training. It is not planned to extract any information about participant and caregiver from these audio recordings.

Any entries on COA should be reviewed for completeness by site staff during the visit and caregiver and participants should be requested to complete any blank items. If a scale cannot be completed during the visit or for a scale the total score (e.g., the composite scores for Vineland™-II) cannot be calculated with the available data, it should be tried to repeat the scale during an unscheduled visit within up to approximately 2 weeks.

Table 4 Overview Clinical Scales/Clinical Outcome Assessments

Scale group	Specific scale	Completed by	Children	Adolescents	Adults	Time [min]
SB5 abbrev. Stanford-Binet		clinician	mandatory	mandatory	mandatory	15-20
ADOS-2		clinician	mandatory	mandatory	mandatory	40-60
CGI-I+CGI-S		clinician	mandatory	mandatory	mandatory	5+5
CY-BOCS-ASD		clinician	mandatory	mandatory	mandatory	~ 20
MERS-R		clinician	mandatory	mandatory	mandatory	15-20
RBS-R		caregiver	mandatory	mandatory	mandatory	~ 15
RBQ-2 [1]	RBQ-2 for Children	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	20-30
	RBQ-2A for adults	participant-reported	---	if deemed appropriate[1] by Investigator based on mental age.	mandatory	20-30
Routine Inventory[1]	CRI-R for Children	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	~ 17
	ARI for adults	participant-reported	---	if deemed appropriate[1] by Investigator based on mental age	mandatory	~ 17
BRIEF	BRIEF for children	caregiver	mandatory	mandatory	---	10-15
	BRIEF-A for adults	caregiver	---	---	mandatory	10-15
Vineland™-II (survey)		clinician	mandatory	mandatory	mandatory	45-60
PedsQL	Family Impact Scale	caregiver	mandatory	mandatory	mandatory	~ 5
	Generic Core & Cognitive Functioning Scales	participant-reported	mandatory	mandatory	mandatory	~10

Table 4 Overview Clinical Scales/Clinical Outcome Assessments (cont.)

Scale group	Specific scale	Completed by	Children	Adolescents	Adults	Time [min]
SSP	Short Sensory profile	caregiver	mandatory	mandatory	-	5-15
Sleep[1]	CSHQ	caregiver	mandatory	mandatory	if deemed appropriate[1] by Investigator	5-10
	PSQI	participant-reported	---	if deemed appropriate by Investigator[1]	mandatory	~ 5
RMET[2]	RMET-C for Children	participant-reported	if deemed appropriate[2] by Investigator	if deemed appropriate[2] by Investigator	if deemed appropriate[2] by Investigator	~ 20
	RMET-R for adults	participant-reported	---	if deemed appropriate[2] by Investigator	if deemed appropriate[2] by Investigator	~ 20
Anxiety[1]	HAM-A	clinician	---	---	mandatory	10-15
	PRAS-ASD	caregiver	mandatory	mandatory	---	~ 10
	BAI	participant-reported	---	if deemed appropriate[1] by Investigator	mandatory	5

1 *For scales where a pediatric and an adult scale or scale version exists, both versions should be administered in adolescents and adults, if deemed appropriate by Investigator. For further details, see protocol Section 8.1.1.3. In any case, at least one scale / scale version will be mandatory.*

2 *For the RMET, either the pediatric or adult version should be administered. If none of the two RMET versions is deemed appropriate for the participant the RMET can be skipped.*

8.1.1.1 Requirements for Caregivers

All disease specific clinical outcome assessments (see Table 4 and Table 1) will take place on-site at the clinic. The same caregiver will provide feedback on all informant-based assessments throughout the study and the same caregiver must attend all on-site visits. If a caregiver visit cannot be completed as arranged – e.g., the caregiver is delayed in transit – visits should be rescheduled as soon as possible after the original appointment. Caregiver-completed assessments cannot be conducted over the telephone. Caregiver initials will be reported on eCRF at all assessments.

The reliable caregiver or parent must live with the participant or have substantial and sufficient periods of contact with the participant and is willing and able to attend the on-site visits when required. The reliable caregiver or parent must oversee the participant's adherence with protocol-specified procedures, and report on the participant's status via completion of study assessments.

If the caregiver is not living with the participant, the Investigator has to be satisfied that the participant can contact the caregiver readily during the times when the caregiver is not with the participant. If in doubt about whether a participant's care arrangements are suitable for inclusion, the Investigator should discuss this with Sponsor (Translational Medicine Leader or designee). A non-cohabitating caregiver must spend sufficient time with the participant so that, in the opinion of the Investigator, the caregiver can reliably

assess the participant's mental status, activities and behavior, and report on the participant's adherence and health. This would normally be possible when the caregiver spends a few hours each day with the participant.

The caregiver arrangements for participants living in a residential home need to be assessed carefully on a case by case basis:

- *A staff member of the residential home can be the caregiver if this person spends sufficient time with the participant. In the opinion of the Investigator, the caregiver must be able to reliably assess the participant's mental status, activities, and behavior, and report on the participant's adherence and health. This would normally be possible when the caregiver spends a few hours each day with the participant.*

- *A family member living at the participant's home can be the caregiver if the participant returns home every night. When the participant returns home only over the weekend, a family member can only be the caregiver if they have intensive interaction with the participant during the week e.g., via phone calls, calls via Skype, SMS messages, etc. The quality of these interactions between caregiver and participant needs to be assessed for each participant to determine whether they are sufficient.*

- *A family member cannot be the caregiver when the participant lives full time in the residential home, unless the family member spends a few hours each day with the participant in the residential home.*

If in doubt about whether a participant's care arrangements are suitable for inclusion, the Investigator should discuss this with the Sponsor (Translational Medicine Leader or designee).

8.1.1.2 *Administration of Participant-reported Scales to Illiterate Participants*

For participants who are illiterate or have reading deficits the following procedure for the mandatory participant-reported scales should be used:

- *The scale administrator will read out the questions and answers and show the answers on the Rater station.*

- *The participant will choose one of the possible answers on the Rater station.*

- *If the participant is still unable to complete the scale even with the described assistance, the scale will be skipped. For adult participants only: where a similar caregiver-reported scale exists, that caregiver-reported scale will be completed instead of the skipped scale if it is deemed appropriate by Investigator (i.e., RBQ-2 if RBQ-2A is skipped, CRI-R if ARI is skipped, CSHQ if PSQI is skipped).*

8.1.1.3 *Administration of both the Caregiver and Participant-reported Scale Version "if deemed appropriate by Investigator"*

For adolescents and adults both versions of the Routine Inventories and the Repetitive Behavior Questionnaires scale should be administered in individual participants at the same visit if the Investigator deems the non-mandatory version of the scale appropriate (see Table 4 and Sections 8.1.1.10 and 8.1.1.11). This includes the participant-reported adult versions (RBQ-2A and ARI) and the caregiver-completed pediatric versions (RBQ-2 and CRI-R).

- *For adolescent participants the caregiver-completed RBQ-2 and CRI-R are mandatory scales. The participant-reported versions RBQ-2A and ARI will be completed as well, if deemed appropriate, and if the Investigator deems the participant able to complete these scales based on mental age.*

- *For adult participants the self-reported versions RBQ-2A and ARI are mandatory scales. The caregiver-reported RBQ-2 and CRI-R will be completed as well, if deemed appropriate by Investigator.*

Similarly, and "if deemed appropriate by Investigator," the caregiver will complete the CSHQ for adult participants- Adolescent participants will complete the participant-reported PSQI and BAI (see Table 4).

If an adult participant is unable to complete a self-reported adult scale (e.g., because of mental age or other reasons) the corresponding caregiver-reported scale version will be used if it is deemed appropriate by Investigator and if such a scale version exists (i.e., RBQ-2 is to be completed if RBQ-2A is skipped, CRI-R if ARI is skipped, CSHQ if PSQI is skipped).

8.1.1.4 Stanford-Binet Intelligence Scale-Fifth Edition (SB5)

The Stanford-Binet intelligence scales fifth edition (SB5) (Roid 2003) is an individually administered test of cognitive abilities and intelligence, designed to assess individuals between 2 and 85+ years of age. The SB5 was also tested in a sample of 63 children with ASD (Coolican et al 2008). The complete SB5 is made up of two subscales with five subtests in each; one measures nonverbal abilities (Nonverbal IQ; NVIQ) and the other measures verbal skills (Verbal IQ; VIQ), which together provide a FSIQ.

For this study only the Abbreviated Battery IQ (ABIQ) of the SB5 will be assessed. The ABIQ provides a quick estimate of two major cognitive factors: fluid reasoning and crystallized ability and the abbreviated SB5 scale consists of two routing subtests: one nonverbal (Object Series/Matrices) and one verbal (Vocabulary). The two routing subtests are administered first, followed by the nonverbal subtests and then the verbal subtests.

The abbreviated Stanford-Binet will take approximately 15-20 minutes to complete.

8.1.1.5 Autism Diagnostic Observation Schedule (ADOS-2)

The ADOS second edition is a diagnostic tool used to document the presence of ASD (Gotham et al 2007; Lord et al 2000). During a semi-structured evaluation, the individual

is observed in a naturalistic social situation and assessed across areas of social communication, imagination, and restricted and/or repetitive behaviors.

The ADOS includes four modules for use with different age groups and language levels; modules 2, 3, and 4 will be used in this study. The appropriate module of the ADOS will be administered by a certified rater at screening.

The assessment will take approximately 35-40 minutes to complete.

8.1.1.6 Children's Yale-Brown Obsessive Compulsive Scale modified for ASD (CY-BOCS-ASD)

The CY-BOCS-ASD is a modified version of the YBOCS, for children with ASD. The obsessions domain is excluded from this version due to the difficulty of obtaining reliable information about obsessions in children with cognitive and language delays. The interviewer asks the parent/caregiver about past and present repetitive behaviors, guided by the revised repetitive behavior checklist (Scahill 2014). It contains a list of 25 behaviors, classified into the following categories: Hoarding/ritualistic behavior, Sensory-motor and arranging, Insistence on routines /Self-injurious behaviors, Stereotypy and Restricted interests. This checklist was expanded from the original version to include repetitive behaviors commonly seen in children with ASD. A target symptom list comprising the four most troublesome behaviors is established by the interviewer. The severity (0 to 4) of each target behavior is rated for the following five items: time spent, interference, distress, resistance and degree of control to generate a total score (0-20). 2 additional items (repetitive behavior-free interval and peculiarity) are also rated but are not included in the total score.

The ratings evaluate the symptom severity over the past week and are based on the information collected from the child and parent/caregiver during the interview. The final rating is based on the clinical judgement of the interviewer.

For any individual participant all CY-BOCS-ASD assessments throughout the study should be done by the same rater.

The interview should take approximately 20 minutes.

8.1.1.7 Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I)

The CGI rating scales are tools used to evaluate both the severity of illness and change from Baseline (Guy et al 1976). The CGI-S reflects the rater's impression of the participant's current autism severity on a 7-point scale ranging from no symptoms (1) to very severe symptoms (7). The CGI-I is used to assess the clinical change as compared to symptoms at Baseline using a 7-point scale, ranging from very much improved (1) to very much worse (7). For this study modified versions will be used (Busner et al 2007 and 1991; Busner et al 1997).

For any individual participant all CGI-S and CGI-I assessments throughout the study should be done by the same clinician.

It will take the clinician approximately 5 minutes to complete the CGI-I and the CGI-S.

8.1.1.8 Montefiore Einstein Rigidity Scale-Revised (MERS-R)

The MERS-R is designed to assess three domains of rigid behavior in children and adults: Behavioral rigidity, cognitive rigidity and Protest (in response to deviations from rigidity) (per personal communication, [redacted] Professor of [redacted]). The MERS-R is a clinician-administered scale in which the clinician uses all available information to rate items (e.g., clinical observations, interview with the subject and/or caregiver, sibling, significant other, etc., clinical judgment, etc.). Each of the domains is assessed separately, during which examples are discussed and related behaviors are probed for to obtain more individualized exemplars. At each visit, new examples of rigid behaviors are elicited because new examples may arise and/or examples may not be realized until they lessen with treatment. A list of relevant behaviors is compiled for each domain, and ratings for the items are based on the average occurrence of the behaviors over the past one week.

For any individual participant all MERS-R assessments throughout the study should be done by the same rater.

The assessment will take approximately 15-20 minutes to complete. The rater will interview the subject and/or caregiver, sibling, significant other, etc. to complete the MERS-R.

8.1.1.9 Repetitive Behavior Scale-Revised (RBS-R)

The RBS-R is a 43-item informant-based questionnaire assessing the variety of RRBs observed in individuals with ASD (Bodfish et al 2000). The scale is grouped into six subscales: Stereotyped, Self-injurious, Compulsive, Ritualistic, Sameness, and Restricted Behaviors.

It will take the caregiver approximately 15 minutes to complete the RBS-R.

8.1.1.10 Repetitive Behavior Questionnaire (RBQ-2)

The RBQ-2 is a 20 items questionnaire to assess the spectrum of RRBs observed in individuals with ASD such as repetitive motor movements, rigidity/adherence to routine, preoccupation with restricted patterns of interest and unusual sensory Interest (Leekman et al 2007; Honey et al 2012). The RBQ-2 exists in two different versions, a caregiver-reported version for pediatric subjects RBQ-2 and a participant-reported version for adults RBQ-2A (Barrett et al 2015).

It will take the caregiver approximately 20-30 minutes to complete the pediatric version of the RBQ-2.

For the adult self-administered version of the RBQ-2A the adult participant will need 20-30 minutes to complete.

8.1.1.11 Childhood Routines Inventory- Revised (CRI-R) and Adult Routines Inventory (ARI)

The CRI-R (for children and adolescents) and ARI (for adults) were developed together and are closely related scales (Evans et al 2017). The CRI-R and ARI questionnaires capture a wide range of RRBs, including stereotypies, tics, compulsions, habits, sensory sensitivities, and focused interests, in the context of typical and atypical development in children, adolescents and adults across the entire lifespan. All items will be answered on a five-point Likert scale from not at all/ never, a little/ rarely, somewhat/ sometimes, quite a lot/ often, and very much / always.

The caregiver-completed CRI-R scale for pediatric subjects includes 62 items. It will take the caregiver about 17 minutes to complete the CRI-R.

The participant-reported ARI scale for adult subjects includes 55 items and will be completed by the participant. It will take the participant about 17 minutes to complete the ARI.

8.1.1.12 Behavior Rating Inventory of Executive Function (BRIEF)

The Behaviour Rating Inventory of Executive Function (BRIEF) parent questionnaire was designed to assess executive functioning of children with a wide spectrum of developmental and acquired neurological conditions, such as: Learning disabilities, Low birth weight, Attention-deficit/hyperactivity disorder, Tourette's disorder, Traumatic brain injury, Pervasive developmental disorders/autism (Gioia et al 2000).

The BRIEF questionnaire for children contains 86 items in eight non-overlapping clinical scales and two validity scales. The BRIEF-A for adult participants, based on the original Behavior Rating Inventory of Executive Function, is composed of 75 items within nine non-overlapping theoretically and empirically derived clinical scales that measure various aspects of executive functioning.

For this study the parent / caregiver versions will be used. It will take the caregiver approximately 10 - 15 minutes to complete the BRIEF for children and adolescents or the BRIEF-A for adult participants.

8.1.1.13 Vineland-II Adaptive Behavior Scales, Second Edition (Vineland™-II)

The Vineland™-II is an instrument that measures communication, daily living skills, socialization, motor skills (only in children up to 6 years) and maladaptive (not assessed in this study) behavior of individuals with developmental disabilities (Sparrow et al 2005). The Survey Interview Form (i.e., semi -structured interview) will be administered to a participant's reliable caregiver in this study, during which the rater or clinician will ask to the caregiver open-ended questions relating to the participant's activities and behavior.

Domain scores will be obtained for the individual domains of Socialization, Communication, Daily Living Skills, and motor skills (up to 6 years only) and used to calculate the Vineland™-II Adaptive Behavior Composite score. Standardized scores on the adaptive behavior composite range from 20-160 with higher scores indicating better adaptive functioning.

For individual participants the same rater should perform the Vineland™-II survey at Baseline and week 12.

This interview will take approximately 45 - 60 minutes. The rater will interview the caregiver to complete the Vineland™-II.

8.1.1.14 PedsQL Family Impact Scale

The Pediatric Quality of Life Inventory (PedsQL™) Family Impact Module version 2 (Varni et al 2004) is a 36-item questionnaire which is completed by the caregiver and was developed to measure parent and family functioning. It encompasses six scales covering 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items), 5) Communication (3 items), 6) Worry (5 items), and two scales measuring parent reported family functioning; 7) Daily Activities (3 items) and 8) Family Relationships (5 items). For each item a 5-point response scale is utilized (0=never a problem; 4=always a problem). Items are then reverse-scored and linearly transformed to a 0–100 scale (0= 100, 1= 75, 2= 50, 3= 25, 4= 0), so that higher scores indicate better functioning (less negative impact).

Scale Scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If more than 50% of the items in the scale are missing, the Scale Score is not computed. A total score, a Parent HRQOL Summary Score, and a Family Summary Score can also be computed by averaging across the relevant domains (total score by averaging across all items, Parent HRQOL Summary Score by averaging the 20 items in Physical, Emotional, Social, and Cognitive Functioning, and the Family Summary Score by averaging eight items in Daily Activities and Family Relationships). The acute form with a recall period of 7 days will be employed in this trial.

It will take the caregiver approximately 5 minutes to complete the PedsQL family impact scale.

8.1.1.15 Pediatric Quality of Life Inventory (PedsQL™) Generic Core & Cognitive Functioning Scales

The Pediatric Quality of Life Inventory PedsQL™4.0 Generic Core Scale assessment consists of a 23 item questionnaire encompassing four core scale domains: Physical Functioning (8 items); Emotional Functioning (5 items); Social Functioning (5 items); and School Functioning (5 items). Additionally the PedsQL Cognitive Functioning Scale which contains six items will also be completed. The acute participant-completed forms

(5 to 7 years, 8 to 12 years, 13 to 18 years, young adults, and adults) with a recall period of 7 days will be employed in this trial (Varni et al 2004).

For children aged 8 years and above, the PedsQL items are scored on a five-point Likert-type response scale (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; and 4=almost always a problem). For children age 5 to 7 years, scoring is based on a three point scale (0=Not at all, 2=Sometimes, 4=A lot). Once scored, items will be reverse-scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better health-related quality of life.

For children aged 5-7 years, an administrator will read out the questions and the child will respond by pointing to one of three smiley faces. Children aged 8 years and above complete the questionnaire themselves. Subjects should complete the same version of the questionnaire throughout the study even if they have moved up an age group.

It will take the participant approximately 10 minutes to complete the PedsQL generic core and cognitive functioning scales.

8.1.1.16 Short sensory Profile (SSP)

The Short Sensory Profile (SSP, Tomchek et al 2007) is a 37-item parent or caregiver-reported questionnaire that probes for the effect of sensory processing anomalies on a person's ability to function in daily life. Item responses occur on a five-point Likert-rating scale from 1 (always occurs) to 5 (never occurs). The Short Sensory Profile was based on the Sensory Profile (Dunn et al 1999) and provides two sets of standard scores depending on how the items are clustered: (1) domain scores (i.e., Auditory, Visual, Vestibular, Touch, Multisensory and Oral Sensory Processing), as well as scores of Sensory Modulation, Behavior and Emotional Response, and (2) factor scores (nine empirically derived factors).

The SSP will be performed for children and adolescents. It will take the caregiver approximately 7 minutes to complete the SSP.

8.1.1.17 Reading the Mind in the Eyes Test (RMET)

In the adult version of the RMET, the RMET-R, the participants are presented a series of 36 pictures of the eye-region of the face of different actors and actresses, and are asked to choose which of four words best describes what the person in the photograph is thinking or feeling. This test was conceived of as a test of how well the participant can put themselves into the mind of the other person, and "tune in" to their mental state. "Theory of mind" is also used as shorthand for the ability to attribute mental states to oneself or another person (Baron-Cohen S et al 2001, Baron-Cohen S et al 2010). The shorter version of the test for children with 28 pictures the so-called RMET-C will also be used in this study (Baron-Cohen et all, 2001b). RMET will be used as anchor data for analysis of digital biomarkers and therefore also healthy participants should complete

the RMET. However at study start it will be decided for each individual participant if the RMET-R or RMET-C should be used or if neither of the two RMET versions is deemed appropriate for the participant. The RMET assessment will take the participant approximately 20 minutes to complete.

8.1.1.18 Child's Sleep Habits Questionnaire Sleep Diary (CSHQ)

The Child's Sleep Habits Questionnaire is a 54-item parent or caregiver-reported measure that enquires about children's sleep habits and possible difficulties with sleep (Owens et al 2000). Parents are prompted to think of their child's life during the past week when answering the questions (or a recent typical week if the past week was unusual). Using a 3-point Likert scale parents indicate whether a behaviour occurs usually (5 or more times a week), sometimes (2-4 times a week) or rarely (0-1 times a week).

The CSHQ will be used for pediatric participants only. It will take the caregiver about 10-12 minutes to complete the CSHQ.

8.1.1.19 Pittsburg Sleep Quality Index (PSQI)

The PSQI assesses sleep quality during the previous month (Buysse et al 1989). It consists of 19 self-rated questions. A wide variety of factors relating to sleep quality are assessed, including estimates of sleep duration and latency and the frequency and severity of specific sleep-related problems. These 19 items are grouped into seven component scores, each weighted equally on a 0-3 scale. The global PSQI score has a range of 0-21 and higher scores indicate worse sleep quality.

Adult participants with a mental age of at least 10 years and adolescents deemed able to complete the PSQI will complete this scale. The entire index requires 5 - 10 minutes for the participant to complete.

8.1.1.20 Hamilton Anxiety Rating Scale (HAM-A)

The HAM-A is a clinician-rated scale to analyze the severity of symptoms of anxiety. The HAM-A consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). The scale is intended for adults, adolescents, and children (Hamilton et al 1959).

The HAM-A will be completed only for adult participants in this study. It will take the clinician-rater about 10-15 minutes to administer the HAM-A.

8.1.1.21 Parent Rated Anxiety Scale-ASD (PRAS-ASD)

The Parent Rated Anxiety Scale for ASD (PRAS-ASD) is a caregiver-rated scale with 25 items to assess the severity of anxiety symptoms in children and adolescents with ASD. Caregivers are asked to describe their child's worries and anxiety-related behaviors over the past two weeks on a 0 to 3-point scale from NONE=not present; MILD=Present

sometimes, not a real problem; MODERATE=Often present and a problem; SEVERE=Very frequent and a major problem. A publication about the PRAS-ASD is in preparation (as per personal communication, Prof Dr. [redacted]).

The PRAS-ASD will be completed for children and adolescents. It takes about 10 minutes for a caregiver to complete.

8.1.1.22 Beck Anxiety Index (BAI)

The Beck Anxiety Inventory (BAI) is a well-validated 21-item participant-administered inventory probing for common symptoms of anxiety (Beck et al 1988). Each item contains four possible responses, which range in severity from 0=not at all (e.g., unable to relax) to 3=severely - it bothered me a lot. Participants are asked to provide answers based on the way they have been feeling over the past month, including the assessment day.

All adult participants will be asked to complete the BAI. Adolescent participants should complete the BAI if deemed appropriate by Investigator for the individual participant based on mental age. The BAI is a self-administered scale and will take the participant about 5 minutes to complete.

8.1.2 Other Assessments

8.1.2.1 Drug Acceptability Survey

For the preparation of subsequent drug interventional studies and to optimize the formulation of study medications for these studies, caregivers *of children (age 5 to 12 years)* will be asked general questions about drug acceptability. For example questions will be asked about preferred color, flavor, size of tablets, and way of administration etc.

For digital biomarker assessments see Section 8.4.1.

8.2 SAFETY ASSESSMENTS

8.2.1 Medical History and Demographic Data

Medical history includes clinically significant diseases experienced up to screening plus for the previous 5 years: developmental history, date of ASD diagnosis, smoking history, use of alcohol and drugs of abuse, medical interventions (e.g., immunizations/vaccines, pharmacological therapies, non-pharmacological therapies, and surgeries [see also protocol sections 6.2, 6.2.1 and 6.2.2]).

Demographic data will include age, sex, and participant-reported race/ethnicity as well as applicable information about residential setting, school or employment status, day care facilities, level of education, participation in educational or day programs, and any non-medical hospitalizations.

General information will also be collected on the caregiver who will oversee the participant's adherence with protocol-specified procedures, and report on the participant's status. This will include, for example, their relationship to the participant, time spent with the participant, and whether they live in the same residence.

8.3 ADVERSE EVENT AND SERIOUS ADVERSE EVENT

The definitions of an AE or serious adverse event (SAE) can be found in Appendix 2. Only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported (e.g., headache related to completion of the scales in this study).

The Investigator and any qualified designees are responsible for ensuring that all adverse events (including assessment of seriousness, severity and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on adverse events at each participant's contact. All adverse events, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

After informed consent has been obtained, only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported (e.g., headache related to completion of the scales in this study*) until the participant has been discharged from the study.*

Post-study adverse events and serious adverse events: The Investigator is not required to actively monitor participants for adverse events after the participant has been discharged from the study.

However, if the Investigator learns of any SAE (including a death) or other adverse events of concern, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related *to a protocol-mandated intervention*, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all participant evaluation time−points.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to Baseline or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.2), or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF-and in the participant's medical record to facilitate source data verification. If, after follow-up, return to Baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

8.3.3.2 Sponsor Follow-Up

For serious adverse events, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants are met.

The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An Investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB and EC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

This section does not apply to this study.

8.3.5 Non-Serious Adverse Events of Special Interest

This section does not apply to this study.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

This section does not apply to this study.

8.3.7 Management of Specific Adverse Events

This section does not apply to this study.

8.4 BIOMARKERS

8.4.1 Digital Biomarkers

At the screening visit, the caregiver will be provided with a study smartphone and wrist-worn wearable with a pre-installed application (also called 'app'). The smartphone will be pre-configured to ensure that the pre-installed app will be accessible by the participant and caregiver, with other apps and settings inaccessible. The app will include a collection of digital biomarker assessments, including surveys and active tests, for the caregiver and participant to complete. The digital biomarker assessments consist of the following:

1) Caregivers and participants will be asked to complete daily reported outcome measures ('surveys') in the smartphone app. Caregivers will be asked a small number of questions each day relating to RRBs, social interactions and symptoms associated with autism. Depending on the participant's ability, the participant will also be asked the same set of questions. Participant ability and specific symptoms will be assessed by the clinician at the screening visit and the app will be configured accordingly.

2) Participants will be assessed with performance outcome measures that will be within the smartphone app ('active tests'). Each active test will be a simple task in the app that lasts 1 to 4 minutes. The tests will assess spatial working memory, emotion recognition, social cooperation and the participant's speech. During the tests, touch interactions will be captured by the smartphone. Audio will be recorded during the speech test. Once a week caregivers will also be asked to record a conversation with the participant that is at least 5 minutes long. Additional people may join this recording, provided they are formally informed by the caregiver. The ability of the participant to complete the active tests will be assessed by the clinician at the screening visit.

The participant and caregiver will receive daily reminders to complete the surveys and frequent reminders to perform active tests.

3) For passive monitoring, the participant will be asked to wear a wrist-worn wearable each day during all waking hours. At their convenience, participants are also encouraged to wear the wearable at night. This device will track the participant's body movements. It may track heart rate. For location tracking, the participant will also be asked to carry the smartphone. Caregivers may be given small transmitters to be placed around the home to facilitate in home location tracking. Participants are asked to charge the devices overnight.

For privacy reasons, no participant-identifying information is recorded. In addition, participants are able to pause the location recording. For the conversation recording, after completing a conversation recording it is possible to delete some or all of that recording.

All data will be transferred to the Sponsor. If participants have a Wi-Fi network at home, they are encouraged to connect their smartphone to enable data transfer. If no Wi-Fi network is available, the sensor data will be transferred during site visits or after the devices have been returned. Data are encrypted and uploaded to secure servers whenever the phone is connected to Wi-Fi.

For storage and analysis of audio recordings the Sponsor will follow, in detail, these guidelines: The raw audio data are encrypted in transfer and at rest (industry gold standard 256-bit asymmetric encryption). For data processing and analysis purposes, the raw audio data need to be decrypted. Decryption only occurs on a designated secure Roche server with tight access control. Access is granted to a named list of researchers only. Access will be limited to as few individuals as possible. The amount of raw audio data that is available in a decrypted format on this server is kept to an absolute minimum. To ensure this, decrypted data are either automatically re-encrypted or deleted immediately after being processed and analyzed. Analysis of the audio data is automated as far as is possible; manual listening to the raw audio data is kept to an absolute minimum. Manual listening will only be done in selected cases as a quality control step for the automated analysis process.

The devices including detailed instructions and training will be provided to the caregiver at the screening visit. Participants will then have a "run-in" period with the device from the screening visit to the Baseline visit. Participants will be instructed to bring the smartphone and wrist-worn wearable to the Baseline visit and each subsequent clinic visit. They will have the opportunity to ask any questions and adherence and technical status of the device will be checked. Also at scheduled phone contacts (see Table 2) site personal will follow-up on progress in collection of digital biomarker data. At each visit, participants will be asked to conduct the active tests under the supervision of a person trained on the digital biomarker approach.

The smartphone and wrist-worn wearable must be returned to the clinic in cases where the participant does not meet eligibility criteria, at the end of the study and upon early termination.

If any part of the digital biomarker assessments is not suitable for the participant, it will be excluded from the participant's schedule of assessments.

At the end of the study or at the time when the participant has completed the study, *both the* participants *and the caregivers* will be asked to complete satisfaction surveys on their experience using the smartphone during the study.

The pre-configured study smartphone and wrist-worn wearable device will be used for data collection and exploratory assessment only. The smartphone and wearable device will not be used in the diagnosis, cure, mitigation, treatment, or prevention of ASD, and no data (except adherence data) is played back to study participants, caregivers or site staff during the study. As such, the smartphone and wearable device are not considered medical devices in this study.

8.5 TIMING OF STUDY ASSESSMENTS

8.5.1 Screening Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms (ICFs) and assent forms for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site.

All screening assessments must be completed and reviewed to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

An Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened participant with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening assessments will be performed *during the* time *window* indicated in the SoA (see Section 1.2), *i.e., within 4 to 2 weeks before the Baseline visit. However, in case of unexpected delays due to logistical or technical reasons (e.g., sickness of caregivers or raters), the screening period may be extended to up to 6 weeks.*

*At screening, t*ests for illicit drugs and alcohol misuse are at the Investigator's discretion. *The Investigator will decide if any tests are required or not to confirm eligibility in context of exclusion criterion #6. In addition, the selection of the appropriate tests and test parameters and the appropriate communication of possible findings to participant and parents according to local regulations will be at the discretion of the Investigator. Roche will support sites in the implementation process should the sites need (e.g., provision of urine dipsticks).*

Note: Any positive tests for amphetamines will need to be reviewed carefully by the Investigator on a case by case basis, because a significant proportion of people with ASD are taking stimulants such as methylphenidate for their attention-deficit problems. In such a case of a misleading drug alert, a possible study participant will not be excluded from the study.

8.5.2 Assessments during Study and Follow-Up Assessments

All assessments must be performed as per SoA (see Section 1.2). After the study completion/early termination visit, adverse events should be followed as outlined in Sections 8.3.1 and 8.3.3.

8.5.3 Assessments at Unscheduled Visits

If a COA (see section 8.1.1) cannot be completed during the visit or for a scale the total score (e.g., the composite scores for Vineland™-II) cannot be calculated with the available data, it should be tried to repeat the scale during an unscheduled visit within up to approximately 2 weeks.

Please see Section 1.2 for activities that are required to be performed in case of an unscheduled visit.

9. STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE JUSTIFICATION

Approximately 90 participants with ASD will be enrolled into six cohorts with approximately 15 participants each by two factors IQ and age:

- IQ: participants with ABIQ $\geq$ 70 vs participants with (ABIQ $\geq$ 50 and $<$ 70)
- Age: children 5 to 12 years; adolescents 13 to 17 years and adults 18 to 45 years

In addition, *45 TD* healthy participants (*15* children *age* 5 to 12 years, *15 adolescents age 13 to 17 years, and 15 adults age 18 to 45 years*) will be enrolled for validation of *digital* biomarkers only.

The sample size was determined by practical considerations and not based on statistical power calculations.

9.2 STATISTICAL ANALYSES

9.2.1 Demographics and Baseline Characteristics

Summaries and listings will be prepared for all relevant Baseline characteristics such as IQ, age, sex, ADOS-2, Vineland™-II, CY-BOCS-ASD, medical history including medications and treatments, caregiver status, educational status of participant and parents, etc.

9.2.2 Safety Analyses

All safety analyses will be based on the safety analysis population defined as all participants who signed the ICF.

Table 5 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.

9.2.3 Statistical methods for the Primary Objectives

All primary endpoints (RRB scales) will be presented by listings and descriptive summary statistics. Additionally, the following properties will be investigated:

- Test/re-test reliability with methods such as displaying Bland-Altman Plots, and calculating intra-class correlation coefficients (ICC) using the Baseline and 2-weeks data by means of an ANOVA model with fixed visit effects.
- Internal consistency with methods such as determining Cronbach's alpha.
- Correlating the Baseline values with the corresponding 12-weeks values.

The structure of missing data and drop outs will be investigated (this will also apply for the secondary and exploratory endpoints).

9.2.4 Statistical methods for the Secondary Objectives

The effect of age and IQ on RRBs in subjects with ASD will be evaluated with graphical displays and by applying regression models with the RRB scale as dependent and age and IQ and other possible covariates

The correlation structure between scales will be evaluated by means of multivariate methods such as principal component analyses and factor analyses

All listed p-values will be interpreted only as descriptive weights and not in a confirmatory sense.

Further details of planned analyses will be provided in the technical document.

9.2.5 Digital Biomarker Analyses

Digital biomarker data will be analyzed for: a) participant adherence; b) agreement between participant/caregiver reports and behavioral data; c) dependence on age and IQ and difference from TD healthy participants.

a) Since digital biomarker data is collected at home, participant and caregiver compliance is an important measure of the success of the approach. Participant adherence will be determined by both completion of daily tasks (surveys and active

tests) and use of the wearable, which can be tracked with sensors that are built into the device.

b) The passive monitoring approaches will be analyzed for agreement with participant/caregiver reports. The focus of the analyses will be on repetitive movements, patterns of movement around the home and beyond, and heart rate signals as these relate to anxiety.

Dependence of the digital biomarker assessment on age and IQ and difference to typical developing controls will be explored.

Further details of planned analyses will be provided in the technical document.

9.3 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for concomitant medication will be listed. The number of participants who were enrolled, discontinued and completed the study will be summarized and listed.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

The following section includes standard appendices: Appendix 1 (for regulatory, ethical and study oversight considerations), Appendix 2 (for AE definitions, reporting). Additional study-related appendices are in order of appearance in the protocol.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant (e.g., advertisements, diaries etc), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all adverse events (as specified) to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

1.3. INFORMED CONSENT/ ASSENT FORMS

The Sponsor's Master Informed Consent Form (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (guardian or caregiver) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act

requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant’s legally authorized representative.

The Consent Forms must be signed and dated by the participant or the participant’s legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant to take part. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the participant or the participant’s legally authorized representative. All signed and dated Consent Forms must remain in each participant’s study file or in the site file and must be available for verification by study monitors at any time.

Participants who are re-screened are required to sign a new ICF.

1.4. CONFIDENTIALITY

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLO).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., scales data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

2.1.2. Clinical Outcome Assessment Data

2.1.2.1 Electronic Clinical Outcome Assessment Data

Participants will use an eCOA device to capture COA data. The data will be transmitted electronically to a centralized database at the eCOA vendor. Entries should be reviewed for completeness during the clinic visit.

eCOA data will be collected using an electronic device provided by an eCOA vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

2.1.3. Preexisting Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

2.1.4. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, COAs (paper or eCOA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.5. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows

preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF/Assents, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Audio recordings will be maintained on a secure server throughout the duration of the study and will be *retained for at least 15* years after study completion. *No records may be destroyed during the retention period without the written approval of the Sponsor.*

For countries where Ethics Committees or the Ministry of Health will not approve audio recording of participant interviews, review of the scale worksheets, submitted as part of the assessment source information, will be performed to verify accuracy of scoring and adherence to study conventions.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

2.3.1. Protocol Amendments

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities (where applicable) in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

2.3.3. Dissemination of Clinical Study Data

A clinical study report containing the results of this trial will be made available to anyone who requests a copy. A description of this clinical trial and a summary of its results will be available at http://www.ClinicalTrials.gov.

2.3.4. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

3. ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor is responsible for the study management, data management, statistical analysis and medical writing for the clinical study report.

4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities (if applicable) if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events Meeting the AE Definition:

- Adverse events that are related to a protocol-mandated intervention.

Events NOT Meeting the AE Definition:

- Abnormal safety assessments which are associated with the underlying disorder, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disorder being studied or expected progression, signs, or symptoms of the disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disorder(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence (i.e., procedural-related):

- **Results in death.**

- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.

- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect** – not applicable for this study.

- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the categories provided in Table 1 (as a guidance for assessing adverse event severity).

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event.

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see above).

3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study mandated procedures, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

4. FOLLOW-UP OF AES AND SAES

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event:

- Serious adverse events *caused by a protocol-mandated intervention only.*

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS

After informed consent has been obtained only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

For reports of serious adverse events caused by a protocol-mandated intervention that occur after the Baseline visit, investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other serious adverse event occurring after the end of the AE reporting period, if the event is believed to be related to protocol-mandated intervention the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to investigators.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

1.1. OTHER ADVERSE EVENTS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between participant evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

4. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to the disorder.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

5. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study and is related to study procedure(s). When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

6. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol.
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The participant has not suffered an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

7. CLINICAL OUTCOME DATA

Adverse event reports will not be derived from COA data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any COA responses suggestive of a possible adverse event are identified during site review of the COA data, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.