Supporting Statement B

The Study to Explore Early Development, Teen Follow-Up Study (SEED Teen)

OMB#

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July 17, 2017

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Section B.1. Respondent Universe and Sampling Methods

SEED Teen is a longitudinal follow-up study of children who participated in the first phase of the SEED case-control study in 2007-2011 when they were 2 to 5 years of age. The purpose of SEED Teen is to collect data on enrolled children's health and development when they are teenagers. Children ages 13-17 years will be identified from four of the six SEED 1 sites in Georgia, Maryland, North Carolina, and Pennsylvania. Data will be collected from three groups of children: children with Autism Spectrum Disorders (ASD), children with other (non-ASD) developmental conditions (developmental disability [DD] comparison group), and children from the general population who were initially sampled from birth records (POP comparison group). Mothers or other primary caregivers of these children will be asked to complete two self-administered questionnaires about their child's health, development, education, and current functioning. One of the questionnaires also includes questions on the caregiver's demographics, health, and relationship with the child.

The data collected in SEED Teen will be combined with data collected during the original SEED case-control study. Thus, SEED Teen provides a unique and rich opportunity to examine the long-term health and developmental trajectory of children in each of the three study groups and how this trajectory might be related to various demographic, maternal pregnancy, and early childhood health and behavioral factors that were collected in the SEED case-control study, 7-13

years earlier.

The SEED Teen sample will be selected from the pool of SEED case-control study participants based on the following three criteria:

- **At completion of SEED case-control study, child was given a final classification of ASD, DD, or POP.**

This criterion excludes children who participated in SEED 1 but were given a final classification of ***POSSIBLE CASE*** *because they dropped out of the study prior to completing the assessments needed to assign a more definitive final classification or because they underwent the aforementioned assessments but the results were indeterminate.*

- **During SEED case-control study, the in person developmental assessment was completed.**

This criterion requires that all children had the necessary developmental assessments to assign a definitive final study classification (see above). Moreover, since the in-person developmental assessment was scheduled as one of the final steps in the multi-step SEED case-control study protocol, this criterion limits the study to those participants who both enrolled in the SEED case-control study ***and*** *completed most study steps.*

- **During SEED case-control study, the primary caregiver gave consent for future follow-up.**

During the SEED case-control study in-person visit, the primary caregiver was asked to sign a consent form that included a separate consent for future follow-up. The verbatim consent language was:

Permission to contact family for future studies (please initial one)

We would like to ask you to allow us to contact you for future studies. If you agree, you will allow us to contact you by mail or telephone to ask your permission to be in another study. These studies would be related to developmental disabilities. These studies may include biologic testing for genetic research.

___ I AGREE to be contacted for future research studies.

___ I DO NOT WANT to be contacted for future research studies.

Table 1 provides sample estimates for children who met these three study sample requirements and will thus be selected for potential recruitment into SEED Teen. Overall, this selected SEED Teen sample is estimated to include 1410 children. Table 2 provides data on key demographic factors for this SEED Teen invitation sample. Because the SEED Teen sample is limited to four of the six original SEED sites, the demographics of the SEED Teen sample are somewhat variable compared to the original SEED 1 case-control study sample from which SEED Teen participants will be drawn. Most notably, the proportion of Hispanic children is much lower in the SEED Teen sample than in the SEED 1 case-control study sample because the two SEED 1 sites ***not*** included in SEED Teen (located in California and Colorado) had much higher proportions of Hispanic children in their populations than the other four sites. As presented in Table 2, in the SEED Teen invitation sample the proportion of mother-child pairs who are Hispanic ranges from 3% to 7% depending on study group. In contrast, in the SEED 1 case-control study final sample, the proportion of mother-child pairs who are Hispanic ranges from

8% to 13%. The other demographic factor that shows notable differences between the SEED 1 case-control study sample and the SEED Teen invitation sample is maternal education. In the SEED Teen sample the proportion of mothers with less than a high school education ranges from 1% to 4%, while in the original sample the proportion ranges from 4% to 8%. Other demographic factors – child sex, birth order, maternal age, and child age – are only modestly variable between the SEED Teen invitation sample and the SEED 1 case-control study sample (data not shown).

While we don't have detailed information on those mother-child pairs originally invited to potentially participate in the SEED 1 case-control study who did not respond to the invitation, mothers who are included in our final SEED 1 case-control study sample tend to be older and more highly educated than both mothers who did not respond to the SEED 1 case-control study invitation and mothers from the general birth cohorts in each study site. However, it is not completely correct to consider those individuals who did not respond to the SEED 1 invitation as true non-responders. It is likely that many of the families invited but never contacted were ineligible for inclusion in the SEED 1 case-control study. While one strength of the SEED 1 case control protocol was inclusion of recruitment strategies designed to enroll participants from diverse and often underserved and understudied population subgroups (as opposed to limiting enrollment to simple clinic-based samples), we nonetheless had to place some restrictions on enrollment into the SEED 1 case-control study because of resource and logistical constraints. Because the SEED 1 case-control study protocol included a control group drawn from birth records within each site's catchment area, eligibility criteria restricted enrollment of potential

ASD and DD cases to those who had been born in the study area for comparability with the control group. Because the SEED 1 case-control study protocol required an in person developmental assessment and biospecimen collection, eligibility criteria further restricted enrollment of potential cases and controls to those still residing in the study area at the time of enrollment. Due to resource limitations, a further eligibility criteria was participant proficiency in English (4 sites) or English or Spanish (2 sites). Other eligibility criteria included ongoing residence with mother or other knowledgeable caregiver since at least 6 months of age who could provide legal consent to participate in SEED and child having adequate vision, hearing and mobility to participate in the SEED developmental assessment. Given that SEED 1 case-control study invitation letters were sent to the family's last known address within the study area and were written in English, it is likely that families who no longer resided in the study area and families whose primary language was not English were disproportionately represented in the group of families we were never able to contact. In fact, even among families who were contacted and agreed to the case-control study eligibility screen, ineligibility rates were high. Across sites, we observed the following in SEED 1case-control study:

Mother-child pairs sampled from birth records for POP group

- Of *potentially* eligible participants sent invitation mailings, study staff had contact with 24%.
- Of those with contact, 34% were found to be ineligible.
- Of those with contact who were found to be eligible, 38% enrolled.

Mother-child pairs identified from health and school sources for ASD or DD groups

- Of *potentially* eligible participants sent invitation mailings, study staff had contact with 29%.
- Of those with contact, 26% were found to be ineligible.
- Of those with contact who were found to be eligible, 56% enrolled.

Table 1. Sample selected for invitation to SEED Teen

SEED Study Classification	GA	MD	NC	PA	Total
ASD	110	91	101	79	381
DD	161	95	183	103	542
POP	133	108	146	100	487
Total	404	294	430	282	1410

Table 2. Sample Teen Invitation Sample Characteristics

Characteristic	ASD	DD	POP
Child sex, %			
Female	18.5	35.1	48.8
Male	81.5	64.9	51.2
Birth order, %			
First	46.5	40.6	44.8
Second or later	53.5	59.4	55.2
Maternal race-ethnicity, %			
Non-Hispanic white	57.1	62.9	74.0
Non-Hispanic black	27.5	26.1	18.1
Hispanic	6.7	4.8	2.9
Asian/Pacific Islander	6.0	2.6	2.7
Other	2.7	3.6	2.4
Maternal age (y), %			
<30	38.8	35.3	32.5
30-34	33.7	36.6	37.3
=>35	27.5	28.1	30.2

Maternal education (y), %			
<12	3.6	1.2	2.5
12	14.1	14.6	7.4
13-15	26.9	22.7	22.8
16+	55.5	56.6	67.3
Child age at time of SEED 1 case-control study (m), mean	60.1	60.8	60.4

As described above, an estimated 1410 families will be sent invitation letters for SEED Teen. The mailing will be followed by an invitation call, during which we will determine whether the child meets the following additional eligibility criteria:

- Child is still living.
- Child's legal guardian (mother or other primary care-giver who participated in the SEED case-control study) is available and willing to participate in SEED Teen.
- Child's legal guardian is familiar with child's health and current activities – and thus is able to accurately complete the study instruments.

The a priori SEED Teen study recruitment enrollment and completion targets are as follows. Each site is expected to:

- Successfully trace and contact a minimum of 60% of SEED 1 participants included in their SEED Teen sample.
- Enroll a minimum of 70% of those participants who are successfully contacted and are determined to be eligible for inclusion in SEED Teen (i.e. 70% response rate).
- Complete data collection activities on 90% of enrolled participants (i.e. 90% completion rate).

As described in part A of this application, we estimate that 80% of those families successfully contacted will be determined to be eligible for SEED Teen. Thus, the minimum final sample of SEED Teen participants is expected to be: 115 ASD, 164 DD, and 148 POP.

With this sample size, we will be able to assess differences between the ASD group and both the POP and DD groups on most health and developmental indicators that have an expected population prevalence of 10% or higher and for which the ASD:POP or ASD:DD prevalence ratio is 2.5 or higher (see Table 3). We will also be able to assess many other health and developmental indicators with 20% or higher population prevalence but lower prevalence ratios. Examples of health outcomes and health care indicators with population prevalence of 10% or higher are:

- Obesity in U.S, children aged 12-19 years in 2011-2014 was 20.5% (**Ogden et al., 2015**)
- ADHD among U.S. children aged 5-17 years in 2011-2014 was 10% (**MMWR Quickstats, 2015)**
- Developmental disability (any type) in U.S, children aged 3-17 years in 2011-2012 was 13.8% (**Schieve et al., 2016**)
- Parental perception of medical home for U.S. children 12-17 years of age in 2011-2012 was 51.4% (**Diao et al. 2017**)
- Currently uninsured among U.S. children 1-17 years of age in 2011-2012 was 27.5% (**Diao et al. 2017**)

While this first phase of SEED might not be sufficiently powered to assess more rare health and developmental indicators, the data collected from this first phase of SEED Teen can be combined with data collected from future phases of SEED Teen.

Table 3. Sample size calculations for analyses under various assumptions of health or developmental indicator prevalence and prevalence ratio comparing ASD vs POP or ASD vs DD

Health, Developmental Indicator Prevalence (% in population)	Prevalence Ratio	Sample Size Needed in ASD Group
5	1.5	1471
10	1.5	686
20	1.5	294
30	1.5	163
5	1.75	714
10	1.75	330
20	1.75	138
30	1.75	74
5	2.0	435
10	2.0	199
20	2.0	82
30	2.0	42
5	2.50	222
10	2.50	100
20	2.50	39
30	2.50	19

All calculations assume 80% power, 5% alpha error, 1:1 ratio ASD vs POP or ASD vs DD.

Section B.2. Procedures for the Collection of Information

Recruitment and data collection for SEED Teen will take place over a three-year period. The exact date of study implementation is dependent on OMB approval, but we expect to begin SEED Teen recruitment by January 2018 and finish recruitment by January 2021. We will

organize our recruitment efforts such that all children are aged 13-17 years of age at the time of recruitment and data collection.

At the completion of the SEED case-control study, each SEED site downloaded and securely saved their study participant tracking data from the centralized web-based data system (CIS) that the Data Coordinating Center (DCC) at Michigan State University has developed and maintained for the SEED case-control study. The DCC has also maintained SEED sites' tracking datafiles in a secure location as a back-up.

The tracking datafiles include participants' complete contact information which was collected at several points during the case-control study data collection protocol:

- Upon enrollment the parent/primary caregiver's contact information was confirmed and updated to include additional telephone numbers used by the parent. Contact information was also obtained for the other parent if s/he was still engaged in child's life.
- At the completion of an early data collection component – a telephone interview with the mother or other primary caregiver – some sites asked the mother/caregiver to provide contact information for someone who would likely always know how to reach her/him (this information was obtained specifically to assist with any future contacts and was stored with the other tracking data for the participant). (Note: some sites did not do this because of restrictions from their IRBs.)
- Throughout the study, contact information was updated as new information became available from the participants.

On average, the minimum contact information available for each SEED participant in the case-control study is parent/primary caregiver address, phone numbers (home, work, and/or cell), and email address. Only limited SEED staff at each site have access to participant contact information. For each participant identified for the SEED Teen sample, the most recently available contact information obtained at the time of the case-control study will be verified to the extent possible using one or more people search engines such as Accurint, United States Postal Service (USPS), White Pages, and/or Google Maps. These search engines can be used to various extents to locate and verify a participant's current street address and phone number. They will also be used to trace potential new contact information for participants who appear to have moved since their last SEED contact. Social networking sites might also be searched as a means of tracing participants.

The preferred first contact for each participant is via an invitation letter. Thus, each site will attempt to ensure they have the most current address for each participant by using one or more of the aforementioned tracing resources. In some instances, it might not be possible to verify the most current address for a participant using these tracing resources. In these instances, SEED staff will attempt to reach out to the participant directly via email or phone call. If that is unsuccessful, staff may reach out to other persons listed by the participant as a potential contact (see above -- SEED case-control study participants at some sites are asked to provide information on contacts who will know how to locate them). SEED staff will call these individuals only to obtain the potential SEED Teen participant's' current address and other

contact information. Staff may generally discuss with these "other contacts" that they were listed as a potential contact during a research study in which the participant previously participated; however, they will not discuss specifics about the participant's involvement in the SEED case-control study or their potential recruitment into SEED Teen.

At each site, SEED Teen staff will select potential study participants based on the eligibility criteria enumerated in Section B.1. They will conduct tracing activities for these participants and create an up-to-date file of the SEED Teen sample contact information. They will send this file to the DCC, using established encryption procedures. The DCC will upload the file into their centralized SEED Teen tracking and data collection system (still to be developed – but with comparable security features as CIS), a web-based system that will be remotely accessible to SEED Teen staff at each site (NOTE: CDC and UNC will only have access to contact and other data from their own study participants; GA SEED participants for CDC and NC, MD, and PA SEED participants for UNC).

The initial contact with each participant will be an invitation letter that is mailed to the primary residence of the prospective participant – i.e. the primary caregiver who completed the SEED case-control data collection activities and signed the consent form for future contact. For most children enrolled in the SEED 1 case-control study, a single caregiver completed study instruments and signed the final consent form. For ~98% of children, this person was the child's biological mother.

However, for a small number of participants, the person who signed the final consent form at the in-person developmental assessment, was not the same person who completed most study data collection components. For example, for some children, the child's mother completed all telephone interviews and self-administered forms ascertaining risk factor, health history, and child development and behavioral characteristics, but the child's father (who was also a legal guardian) accompanied the child to the in-person developmental assessment and thus, signed the final consent forms during that visit. In these instances, we will contact the caregiver who was most actively engaged with data collection activities in the SEED case-control study. The initial SEED Teen mailing will be sent to the parent or other caregiver who completed the majority of the data collection components even if this person did not provide the final written consent. In this regard, it is important to note that the person who participated in the enrollment call for the SEED case-control study, would have nonetheless provided verbal consent for the study during that call and would have been sent an enrollment packet which included a copy of the full consent form that was to be signed by the legal guardian/caregiver who attended the in person visit.

The invitation packet (**Attachment 3**) will be sent from the study site via USPS and will be written in English. The four SEED sites included in SEED Teen only enrolled English-speaking participants in the case-control study. The invitation packet will include:

- A letter (each will be personalized to include the invitee's name) (**Attachment 3.a**) introducing the study and including the following:
    - Brief statement of the study purpose

- Brief description of the what the participant will be asked to do
- Description of monetary incentive
- Brief statements regarding the voluntary nature of study and protection of participant confidentiality
- Description of the ways the invitee can contact the site directly: mail enclosed response card to site, site telephone number, site email address and at UNC, a site website that allows participant to enter their contact information
- Statement informing the prospective participant that the site will follow-up soon with a phone call
- A response card and pre-paid envelope that the invitee can return indicating interest and updating contact information if necessary (**Attachment 3.b**)
- Each site might also use additional invitation materials:
    - A site-specific incentive (e.g., magnet or key chain) valued at approximately $2.00 or less (current federal guidelines for use of federal funds will be followed in deciding whether to include this type of incentive in the invitation mailing).
- UNC might also include:
    - A postcard sent in advance of the Invitation Packet to serve as a "heads up" to the recipient to look for a future invitation letter (**Attachment 3.c**).

If a valid mailing address for a potential invitee is not obtainable or is for some reason questionable (e.g., initial mailing to last known address is returned to SEED site as

undeliverable; or contact with persons at the most recent address indicates the invitee no longer lives at that location), the study staff will attempt to contact the participant via phone or email. If email is used, a brief message similar to the invitation letter will be sent (**Attachment 3.d)**.

If the potential participant indicates at any point that s/he is not interested in further contact, no further contact will be attempted. A negative response includes: sending a text or email to the study site indicating that s/he does not want to be further contacted; calling the study site number and leaving a similar message; indicating to a staff member during a follow-up phone call that s/he does not wanted to be contacted again.

For most potential participants, the invitation call will follow the invitation letter. However, for some participants for whom a valid address could not be located, the invitation call will be the first contact. If a letter was sent, and there was no response from the potential participant to the letter, the invitation call will occur no sooner than 14 days after the invitation letter was sent. If the potential participant, after receiving the invitation letter, reaches out directly and contacts the SEED site via phone, email, or returned response card (**Attachment 3.b**), the invitation call will occur as soon as possible after the participant contact.

The appropriate respondent on the invitation call is the specific invitee sent the invitation letter – or in absence of an invitation letter, the person determined to be the invitee a priori based on SEED case-control study respondent. If the person contacted on the call is not the invitee, the SEED staff will ask for the invitee. If the invitee no longer lives at the residence or uses the

phone number called, the SEED staff will ask for the invitee's current contact information and simply explain that s/he would like to talk to this person about a health study. Care will be taken in how this is approached in order to avoid a breach of confidentiality (e.g., staff will not discuss the invitee's prior participation in SEED case-control study). If more than one caregiver participated in the SEED case-control data collection – see example above where one caregiver completed interviews and self-administered forms and another accompanied child to the in person developmental assessment visit – the SEED staff may provide information about the study to either caregiver available. SEED staff will not discuss the prior SEED case-control study with anyone who was not an involved in data collection activities for that study, unless we are given explicit permission to do so (see below).

The flow of the screening and invitation phone call will vary depending on the respondent and whether or not s/he received the invitation packet. A call script has been developed and will serve as a detailed guide to the SEED staff conducting the call (**Attachment 4**). Calls will include the following components in the following preferred order:

1. Interviewer introduces themselves and confirms that respondent is the correct invitee.
2. Brief discussion thanking respondent for past participation in SEED case-control study and providing a brief recap of the consenting process for that study – i.e. to describe that we are only contacting participants who previously gave permission for future contact.
3. Brief introduction to SEED Teen and request to conduct eligibility screen.
4. Conduct the eligibility screen. In sum to be eligible for SEED Teen:
    a. The child must still be living.

b. The child must still have a legal guardian available to participate in the study.

c. The child should be currently residing:

    i. with a legal guardian OR

    ii. with another adult but legal guardian is still actively engaged with child (see 4d below) OR

    iii. in a residential facility for youth with disabilities but legal guardian is still actively engaged with child (see 4d below).

Children currently residing in a juvenile detention facility or in foster care are not eligible for SEED Teen.

d. The child's legal guardian must be familiar with child's health, health care, education, and current activities – and thus able to accurately complete the study instruments.

This criterion is meant to specifically address situations in which the child has a parent/legal guardian who agrees to participate but that person is not currently residing with the child. Rather, the child is living in a residential facility or in another household. In many cases the legal guardian will still be actively engaged in all facets of the child's life and will be able to complete the survey instruments even though the parent and child don't reside together. But in some cases, the parent/legal guardian will not be engaged to the level that they will be able to

answer detailed questions about the child's health and development. These children will be ineligible for SEED Teen.

5. If from the eligibility screen it is determined that the SEED Teen invitee is no longer the sampled child's caregiver/legal guardian, the SEED staff will query the respondent to determine if the child is still living in a situation that might render him/her eligible for SEED Teen.

   For example, the original invitee, i.e. caregiver who completed data collection activities for SEED case-control study, might be the child's grandmother. During the invitation call with the grandmother, she indicates that she is no longer the primary caretaker and legal guardian; the child currently resides with his mother who is now the legal guardian.

   In situations such as this, the SEED staff will ask the original invitee's permission to contact the new caregiver/legal guardian and if permission is granted, the staff will ask for that person's contact information. Alternatively, if the original invitee is not comfortable providing the person's contact information, we will ask that s/he pass along our contact information to the new caregiver/legal guardian. The call would end and the new caregiver will be contacted –by invitation letter first if possible -- OR we will wait for the new caregiver to make contact with via the study phone number, email, or website.

If in a situation, such as the one described above, the original invitee does NOT grant permission to contact the new caregiver/legal guardian, the child will be considered ineligible. We will not contact a new legal guardian without explicit permission from the SEED case-control study caregiver participant.

6. Once the correct invitee is contacted and the child is determined to be eligible for SEED Teen, the SEED staff will provide a more detailed explanation of the study including a discussion of the two SEED Teen data collection instruments – SEED Teen Health and Development Survey and the Social Responsiveness Scale. The description will include a brief overview of content and estimated time needed to complete each instrument.
7. Staff will discuss the incentive of $30 cash card or money order the participant will receive as a thank you (**Attachment 8**) for their participation in SEED Teen once the data collection instruments are completed.
8. Staff will describe data collection mode. The preferred data collection mode is self-administered. Both data collection instruments will be mailed to the parent/guardian who will complete the forms and return to the study staff via mail. However, if the parent/legal guardian prefers, SEED staff will complete the forms via telephone interview.
9. Staff will also discuss two optional supplemental components of the SEED Teen protocol:
    a. Consent [and assent] to maintain contact with SEED Teen participants for possible future follow-up studies when they reach adulthood.

b. Consent and assent to share genetic data obtained from biosamples collected in the SEED case-control study with genetic research consortiums established and maintained by the National Institutes of Health (NIH).

   This latter request will only be discussed with those participants for whom child biosamples were collected during the SEED case-control study AND who consented that these biosamples could be stored with identifiers (estimated to be 82-86% of SEED 1 participants in the final SEED Teen sample, depending on study group). For these participants, staff will discuss that since the original SEED data collection, there have been several national efforts overseen by the NIH for researchers to share their findings from their studies on genes and autism in order to speed the progress of scientific discoveries.

   Respondents will be told that the decision about whether to provide us with consent for genetic data sharing or future follow-up contacts is completely optional, that if they choose NOT to consent to either genetic data sharing or future follow-up contacts, that decision will in no way impact their participation in SEED Teen and that they will receive the $30 incentive for SEED Teen regardless of their decisions to provide these two supplemental consents.

10. Staff will answer any questions.
11. Staff will ask the respondent for verbal consent to participate in SEED Teen. As part of

the verbal consent process, staff will explain that participation in SEED Teen is voluntary nature and will describe the measures SEED sites will take to protect respondents' and children's privacy and confidentiality.

12. Staff will review contact information with staff, obtain any additional contact information available, and confirm address to send the SEED Teen data collection packet.

If at any time the invitee expresses concerns about the study, s/he will be referred to the site's principal investigator or his/her designee.

Invitees who decide not to participate in SEED Teen will be asked if they will consider consenting to genetic data sharing (if they have provided consent to store their child's biospecimens with identifiers).

Invitees who decide not to participate in SEED Teen who either do not have biospecimens stored with identifiers or who indicate they are not willing to consider consenting to genetic data sharing will receive no additional contact.

The data collection packet will be sent to the participant via USPS or FedEx (site specific) as soon as possible after enrollment. SEED staff will call the participant a week after the packet is sent to confirm receipt, answer any questions, and if the participant's preference is to complete the SEED Teen instruments over the phone rather than completing them on their own, the staff

will either work with the participant during the call to complete the instruments or set up a separate call to complete the instruments.

Staff will tell the participant to plan for a 90-minute data collection time if the phone option is chosen. Although we estimate that on average, it will take 55 minutes for participants to complete both forms on their own, phone administration will take longer. Also, the time to complete the SEED Teen Health and Development Survey is variable depending on the child's health conditions and needs and disability status. Additionally, if the phone option is chosen for SEED Teen instrument administration, the participant might also require some help with the two supplemental consent forms. Participants must sign and return those forms in order for their consent to be valid, but some participants might need help in understanding the forms before they sign them.

The full data collection packet (**Attachment 6**) will include:

1. Cover Letter (**Attachment 6.a**)
2. Participant Information Sheet (**Attachment 6.b**) which includes:
    - Rights of Research Participants
    - Frequently Asked Questions About SEED Teen
3. Tape measure – to measure child's height for the SEED Teen Health and Development Survey
4. SEED Teen Health and Development Survey (**Attachment 6.c**)
5. Social Responsiveness Scale (**Attachment 6.d**)

6. Consent Form for Future Contact (**Attachment 7.a**)
7. Consent Form for Genetic Data Sharing (**Attachment 7.b**)
8. Prepaid envelope to return SEED Teen Health and Development Survey, Social Responsiveness Scale, and supplemental consent forms.

If the participant's SEED 1 case-control study data collection did not include child biosamples or if the caregiver did not consent to storing child's biosamples with identifiers, the genetic data sharing consent form will not be included in the packet.

If during the invitation call the participant indicates s/he does not wish to receive either the future contact consent form or the genetic data sharing consent form, those forms will not be included in the data collection packet.

Once the data collection instruments are returned to the SEED site or upon completion of the instruments over the phone with SEED staff, a Thank You letter (**Attachment 8)** will be sent to the participant via USPS or FedEx (site specific). The thank-you mailing will include the $30 cash card or money order (site specific).

If only one SEED Teen instrument is returned, staff will follow-up with the participant to discuss the missing form (to ensure it was not omitted in error). If the participant indicates s/he does not wish to complete the second instrument, s/he will be sent the Thank-You letter with the full $30

incentive. We will not penalize subjects for choosing NOT to complete some questions on either form or an entire form.

If the supplemental consent forms are not received, staff will also follow-up and request the participant return the forms even if they choose not to provide consent. Both forms include options for the participant to specifically indicate they do NOT consent. We will ask the participant to return all forms for our records. However, if participant states they s/he does not wish to provide consent and also does not wish to return the forms, the staff will indicate in the SEED Teen tracking system that the participant verbally indicated no consent for future contact and/or genetic data sharing.

If the participant returns/completes either SEED Teen instrument s/he will be sent the Thank-You letter and full $30 incentive whether or not they return the consent forms.

In the event that one or both of the SEED Teen data collection instruments is not returned to the study, study staff will attempt to contact the family up to 8 times by telephone (or email if that is the optimal mode of contact) over a six-month period to complete data collection or receive confirmation that the participant does not wish to complete data collection. The contact schedule is as follows:

- Over a 1-2 month period: 1 morning call, 1 afternoon call, 1 evening call, 1 weekend call
- No call attempts will be made for the following 1-2 months.

- Over the next 1-2 month period: 1 morning call, 1 afternoon call1, 1 evening call, and 1 weekend call.

Separate from the 8 phone attempts, a participant may receive a passive refusal letter after 4 cancellations of scheduled telephone appointments to complete study instruments even if the call is re-scheduled. Sites may decide on a case-by-case basis when to send a passive refusal letter to such participants.

After the 8 contacts have been attempted without success or 4 or more data collection appointments have been cancelled:

- If the participant returned one but not both instruments, SEED staff will send the Thank You letter (**Attachment 8**) and $30 cash card or money order as described above. No further contact will be attempted.
- If the participant did not return either study instrument, SEED staff will send a Passive Refusal letter (**Attachment 9**), via regular mail or email that indicates we will no longer attempt to make contact with the participant.

Section B.3. Methods to Maximize Response Rates and Deal with Nonresponse Bias

In contrast to the challenges faced in accurately determining response rates for original SEED case-control study, we will be able to more readily calculate response rates for SEED Teen given we have a much more clearly defined sampling frame – previous SEED participants who

completed all study steps. Moreover, a further eligibility criteria is that the parent/caregiver respondent in the SEED 1 case-control study must have provided consent to be contacted in the future. Thus, we are starting with a motivated target population for SEED Teen.

While we have kept in touch with families by sending periodic newsletters (unless they opted out of these mailings), we have not actively followed them to ensure we have current contact info. We anticipate that our biggest barrier to study response is loss to follow up because we are unable to locate participants who have moved. Study staff will utilize tracing procedures to locate the most recently available contact information for study participants. One or more people search engines such as Accurint, USPS, White Pages, and/or Google Maps, as well as social networking sites, will be used. These search engines will also be used to trace potential new contact information for participants who appear to have moved since their last SEED contact.

Given the diversity of our study population, we need to be mindful that some participants have low literacy level and this might pose a barrier to participation in a study in which participants are asked to complete self-administered forms. To minimize this barrier, study staff will tell participants during the invitation call that they will be available to help study participants complete their data collection instruments over the phone rather than using the self-administered mode.

Finally, respondents will be told they will receive a $30 cash card or money order (site specific) as a token of appreciation after they have completed and returned the study instruments.

While we expect non-response to be minimal, we have comprehensive data on all children who will be initially sampled for invitation to SEED Teen (from all 4 sites). Therefore we will be able to compare responders to non-responders on socio-demographic and child health and development factors that were collected as part of SEED 1.

Section B.4. Tests of Procedures or Methods to be Undertaken

The two data collection instruments in SEED Teen are the SEED Teen Health and Development Survey (**Attachment 6.c**), and the Social Responsiveness Scale (**Attachment 6.d).**

The SEED Teen Health and Development Survey was developed by study investigators to collect information on the following domains:

- Child's health (See section A of SEED Teen Survey)
- Child's health care services (See section B of SEED Teen Survey)
- Child's education (See section C of SEED Teen Survey)
- Child's developmental services (See section D of SEED Teen Survey)
- Child's abilities, strengths, and difficulties (See section E of SEED Teen Survey)
- Child's activities (See section F of SEED Teen Survey)
- Child's safety and stressful life events (See section G of SEED Teen Survey)
- Caregiver expectations for child (See section H of SEED Teen Survey)
- Information about the caregiver and family (See section I of SEED Teen Survey)
    - Demographics
    - Health
    - Community
    - Relationship with child
- Household information (See section J of SEED Teen Survey)

Nearly all questions (97%) in the SEED Teen Health and Development Survey instrument were selected from existing child health and development surveys or study questionnaires or adult

surveys (for questions on caregiver, family, and household). These question sources include the following instruments:

- National Survey of Children's Health (NSCH) (https://www.cdc.gov/nchs/slaits/nsch.htm)
- National Health Interview Survey (NHIS) (https://www.cdc.gov/nchs/nhis/)
- National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/)
- Pregnancy Risk Assessment Monitoring System (PRAMS) (https://www.cdc.gov/prams/)
- Behavioral Risk Factor Surveillance System (BRFSS) (https://www.cdc.gov/brfss/)
- Infant Feeding Practices Study II (IFPS 11) and Year 6 Follow-Up (Y6FU), a U.S. nationally distributed longitudinal study of maternal health and infant health and feeding practices (https://www.cdc.gov/breastfeeding/data/ifps/index.htm)
- National Longitudinal Transition Study-2 (NLTS2) (http://www.nlts2.org/)
- Interactive Autism Network (IAN) (https://iancommunity.org/)
- SEED case-control study maternal and child health history forms

Additionally, two standardized scales previously validated and used in numerous studies were embedded in the instrument:

- Waisman Activities of Daily Living (W-ADL) Scale (18)
- Strengths and Difficulties Questionnaire (SDQ) (19)

For most of the above instruments, extensive pilot and field testing was completed when the instruments were developed; additionally, all have been previously fully implemented in other surveys or research studies and thus offer benefits of having been scrutinized in light of past researchers' experience analyzing the data. In order to implement this first phase of SEED Teen within a 5-year funding cycle and collect data from participants when their children were aged 17 years or younger, the SEED Teen investigators faced a compressed timeline (which includes OMB review and approval) to develop the SEED Teen Health and Development Survey. We therefore were very mindful of the need to utilize the vast experience of other researchers who have previously developed and thoroughly tested questions that covered our research domains.

Moreover, many of the questions we used are from surveys of nationally-representative samples of US children. This holds an added benefit of allowing us to compare SEED Teen data obtained from all three study groups – ASD, DD, and POP – to external prevalence rates for health indicators in US children in the general population.

In compiling questions into a single SEED Teen instrument, we made only minor revisions to some of these existing questions. We made small non-substantive revisions such that we used the same verbiage style throughout the SEED Teen instrument. For example questions from various instruments used different phrasing to describe time period of interest, such as "DURING THE PAST 12 MONTHS" or "DURING THE PAST YEAR", or "IN THE LAST YEAR" and have typically placed this verbiage either at the beginning or the end of a question. In the SEED Teen instrument, we revised all applicable questions to use consistent phrasing, "DURING THE PAST 12 MONTHS" (or other timeframe of interest) and our default placement was the beginning of a question. In some instances we added an option to a multi-option question. For example we added an option on "use of special diet to help with behavioral problems" to a question on complementary and alternative health care treatments because we know this is a common alternative treatment used by families of children with developmental disabilities. We also changed the timeframes on a few questions to collect appropriate data for this population of children. We developed very few truly new questions; we only developed new questions to capture information for which we could not find a suitable existing question. But

even for these questions, we modelled the question verbiage on other existing questions of similar topics to the extent possible.

The SEED Health and Development Survey has been evaluated by less than 10 CDC staff to ensure appropriate skip patterns and determine the time required for completion. This survey represents new survey material for data collection. Our internal testing of the time to complete the survey indicated a range of 25 to 45 minutes depending on the complexity of the child's health and developmental status with an average completion time of 35 minutes. Additionally, the first two questions on the SEED Health and Development Survey, ask participants to measure their child's height with a tape measure (provided in the data collection packet) and weigh their children on scale in their home if possible. We estimate it will take an additional 5 minutes to complete these measurements bringing the total average completion time for this instrument to 40 minutes.

The second SEED Teen instrument, the Social Responsiveness Scale (20), is a 65-item dimensional measure of the severity of ASD symptoms as they occur in natural social settings. It provides a total score reflecting severity of social deficits in the autism spectrum, as well as five treatment subscale scores: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior.

The SRS holds several advantages for use in SEED Teen. It provides an in depth measure of social developmental characteristics. It can be completed in a reasonable timeframe (estimated

time to complete is 20 minutes). The SRS instrument was included in the SEED case-control study, thus allowing for a direct comparison and assessment of the child's trajectory on a core developmental component of importance in assessing ASD. And it is also a valid and useful measure of social development for all children, not only those with ASD; thus this instrument can be used to obtain important data on all three SEED study groups.

Section B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

SEED Teen is a collaborative effort between the CDC, National Center on Birth Defects and Developmental Disabilities (NCBDDD) and one extramural Centers for Autism and Developmental Disabilities Research and Epidemiology (CADDRE) center, the University of North Carolina at Chapel Hill (UNC). CDC will collect data from the Georgia SEED site. UNC will collect data from the North Carolina SEED site. UNC has partnered with two other CADDRE sites that participated in SEED 1 (Johns Hopkins University and the University of Pennsylvania). Under agreements with these two institutions, UNC will collect data from SEED 1 participants from the Maryland SEED site and Pennsylvania SEED site in addition to the North Carolina SEED site. Scientists and clinicians from the four SEED sites have jointly developed the SEED Teen protocol. The individuals leading these efforts at each site are:

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In addition to providing extramural funding to UNC, NCBDDD is also supported through contracts with Research Triangle Institute (RTI) International, Acentia, Carter Consulting, Inc., and McNeal Professional Services. The RTI, Acentia, and Carter Consulting, Inc. staff members

are integrated with CDC staff and work on this and other projects on site at CDC in the Developmental Disabilities Branch (DD Branch), NCBDDD. They will be responsible for collecting data for SEED Teen in Georgia.

Analysis of SEED Teen data will be joint responsibility of the CDC/NCBDDD and UNC. The existing SEED Analysis and Publication Guidelines will be updated to incorporate policies for SEED Teen data analyses. CDC and UNC will work together to develop this SEED Teen update. Guidelines for SEED Teen will be modelled after the existing guidelines for the case-control study.

The findings from analyses of SEED Teen data will be published in peer-reviewed journals and presented at scientific, stakeholder, and public community conferences and meetings. Data will be presented in aggregate in a manner that preserves participant confidentiality.