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Agency for Toxic Substances and Disease Registry (ATSDR)

"Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): Multi-site cross-sectional study"

The Multi-site Study

Manual of Procedures

April 24, 2020

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1.0 Introduction

This Manual of Procedures (MOP) is a handbook that details this study's conduct and operations as well as facilitates consistency in protocol implementation and data collection across study participants (and sites). It transforms the study protocol into a guideline that describes each step of the study and how it is to be executed. The MOP is provided to each member of the Study Team. The MOP contains an adequate amount of detail that study staff and contractors (at all sites) could run the study consistently with only the information contained in the MOP and its appendices. The Study Team (NCEH/ATSDR staff and contractors) must be aware of the terms of award, required reporting, and data and safety monitoring.

- The Multi-site Study Protocol 7207.0 was approved by the CDC Institutional Review Board (IRB) on 04/04/2019.
- A Certificate of Confidentiality (CoC) has been issued for this study. A CoC is a special privacy protection to help researchers protect the privacy of people enrolled in sensitive health-related research.
- The Office of Management and Budget (OMB) approved the information collection request (ICR) under the Paperwork Reduction Act (PRA) on xx/xx/2019 (OMB Control No. 0923-xxxx, expiration date xx/xx/20xx).
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2.0 Brief Overview of the Study Protocol

In response to growing awareness of the extent of PFAS contamination across the U.S., the Section 316(a) of the 2018 National Defense Authorization Act (P.L. 115-91) authorized the Agency for Toxic Substances and Disease Registry (ATSDR) to conduct a study on the human health effects of PFAS contamination in drinking water. The existence of widespread contamination at many sites around the U.S. makes this a paramount effort in addressing the health effects of exposures to PFAS from contaminated drinking water. Consequently, ATSDR is requesting a three-year Paperwork Reduction Act (PRA) clearance for the Multi-site Study. The Multi-site Study will build on the preceding proof-of-concept study at the Pease International Tradeport in Portsmouth, New Hampshire (OMB Control No. 0923-xxxx; expiration date mm/dd/yyyy).

ATSDR will conduct this research using a cooperative agreement titled "Multi-site Study of the Health Implications of Exposure to PFAS-Contaminated Drinking Water" (Notice of Funding Opportunity [NOFO] No. CDC-RFA-TS-19-002). The expected number of research recipients (e.g., entities selected for funding) is six. The program will be administered by the CDC Extramural Research Program Office (ERPO) at the National Center for Injury Prevention and Control (NCIPC). The research under this cooperative agreement will be a two-part program. First, a mandatory core research protocol for all recipients is designed to aggregate data across all sites and designed to compare data between sites. Next, each recipient will have the option to propose additional investigator-initiated research questions and hypotheses related to the overall goals of this NOFO.

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The main goal of this cross-sectional multi-site study is to evaluate associations between measured and reconstructed historic serum levels of PFAS including PFOA, PFOS, and PFHxS, and selected health outcomes. The health outcomes of interest include lipids, renal function and kidney disease, thyroid hormones and disease, liver function and disease, glycemic parameters and diabetes, as well as immune response and function in both children and adults. In addition, the study will investigate PFAS differences in sex hormones and sexual maturation, vaccine response, and neurobehavioral outcomes in children. In adults, additional outcomes of interest include cardiovascular disease, osteoarthritis and osteoporosis, endometriosis, and autoimmune disease.

Under the cooperative agreement, each recipient shall propose candidate study sites at communities whose drinking water was impacted by AFFF use or by industrial PFAS emissions. Site selection will consider the documented levels of PFAS drinking water concentrations. The aim will be to include sites so that a wide range in PFAS exposures levels are included in the study. This will enable the evaluation of exposure-response trends including effects at the lower range of exposures. Ground water contaminant fate and transport models and water system distribution system models may be necessary to identify the areas with contaminated drinking water, to determine the period when the drinking water was contaminated, and to reconstruct historical PFAS contaminant concentrations.
For exposure estimation, participants will be categorized based on their measured serum concentration of PFAS compounds or on modeled estimated historical serum levels (e.g., referent or low, medium, high). Measured and estimated PFAS serum levels will also be evaluated as continuous variables. At sites with prior PFAS biomonitoring data, the study will evaluate changes in PFAS concentration over time.

Each recipient shall reconstruct historic serum PFAS concentrations. This may be done by estimating half-lives and elimination rates as well as by water contamination modeling to inform pharmacokinetic (PK) or physiologically based pharmacokinetic (PBPK) models. Historical serum PFAS reconstruction will enable the evaluation of exposure lags and vulnerable periods as well as statistical analyses that can control for confounding and reverse causation due to physiological factors.

Each recipient shall identify and enumerate all households served by the contaminated drinking water supply in the selected community to recruit potential participants and to meet the sample size requirements for children and adults. If the selected community is served by a PFAS-contaminated public water system, then the recipient will obtain a list of households served by the water purveyor from its billing records. If the community is served by contaminated private wells, then the recipient will obtain a list of households with contaminated wells from the local and/or state health and environmental agencies.

Statistical sampling methods (e.g., a two-stage cluster sample) may be used for recruitment of study participants if all the affected households can be enumerated. If the PFAS drinking water concentrations vary widely across the community, then the recipient should consider using targeted sampling approaches - including oversampling of areas with higher PFAS concentrations - to ensure a sufficiently wide distribution of exposure levels among study participants to evaluate exposure-response trends. If enumeration of all households is not feasible, or if participation rates are expected to be low, then the recipient can consider non-probabilistic sampling approaches such as “judgment” and “snowball” sampling approaches.

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The recipients should consider requesting assistance from local and state health departments in its recruitment efforts. In addition, the recipient should engage community organizations to assist in conducting outreach about the study and recruitment of participants and consider establishing a community assistance panel (CAP). The CAP could provide comments on any additional investigator-initiated research questions and hypotheses and facilitate the involvement of the affected community in decisions related to outreach about the study, participant recruitment strategies, and study logistics.

The CAP could also assist the recipient in the dissemination of study findings to the community.
In total, ATSDR seeks to enroll at least 8,000 participants (6,000 adults and 2,000 children and their parents) from communities exposed to PFAS-contaminated drinking water over the first three years of the five-year cooperative agreement program. To restrict this study to drinking water exposures, adults occupationally exposed to PFAS will not be eligible for the study (e.g., ever firefighters or ever workers in an industry using PFAS chemicals in its manufacturing process). Likewise, children whose birth mothers were occupationally exposed will not be eligible.

At enrollment, each recipient will obtain adult consent, parental permission, and child assent before data collection begins. For each participant, the recipient will take body measures, collect blood samples to measure PFAS serum levels and several effect biomarkers such as lipids, and thyroid, kidney, immune and liver function. The recipient will also obtain urine samples from participants to measure PFAS levels and kidney function biomarkers. The study will archive leftover serum and urine samples for additional analyses of PFAS chemicals and specific effect biomarkers. The National Center for Environmental Health (NCEH) laboratory will perform blood and urine PFAS analyses for all Multi-site Study participants. Thus, issues of inter-laboratory variability for exposure measures will be eliminated.

Adult participants and a parent of child participants will complete a questionnaire that includes residential history, medical history, occupational history, and water consumption habits (n=2,000 adults and 667 children per year). Ideally, the parent will be the child's birth mother, as ATSDR will ask details about the child's exposure, pregnancy, and breastfeeding history.

3.0 Study Staff Responsibilities

The Study Team responsibilities are described in this section.

The Principal Investigators and NCEH/ATSDR staff perform duties of both the study site and of a data coordinating center and the following responsibilities:

- Developing all study materials including the MOP and study forms
- Protecting participants' rights
- Submitting documents to regulatory bodies (i.e., IRB, OMB)
- Ensuring compliance with regulatory requirements (i.e., IRB, OMB)
- Developing and implementing:
  - ✓ Data management procedures including the data flow and procedures for data entry, error identification and correction
  - ✓ Quality control procedures

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  - ✓ Reports - enrollment, participant status (e.g., withdrawals), adverse events, independent safety monitoring body reports
- Reporting and monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Data analysis
- Manuscript writing and publication

The site contractor staff perform the duties of both the study site and of a data coordinating center and the responsibilities include the following as relevant:

- Ensuring compliance with regulatory requirements (i.e., IRB, OMB)
- Protecting participants' rights
- Recruiting, screening, and enrolling of participants
- Obtaining informed consent from each participant
- Collecting study data and following participants through study completion
- Implementing:
  - ✓ Data management procedures including the data flow and procedures for data entry, error identification and correction
  - ✓ Quality control procedures
  - ✓ Data delivery
  - ✓ Reports - enrollment, participant status (e.g., withdrawals), adverse events, independent safety monitoring body reports
- Reporting and monitoring of Adverse Events (AEs) and Serious Adverse Events (SAEs)
- Data analysis
- Manuscript writing and publication

4.0 Recruitment

4.1 Study Roll Out and Communication Plan

The recipient will work with local and state health and environmental agencies as well as local and state-wide community groups in conducting outreach to encourage participation in the study. The recipient may establish a community assistance panel (CAP) at each site, (or covering several nearby sites), to assist in outreach efforts. The recipient may also establish a multi-site "umbrella" CAP, with community representatives from each of the sites included in the study, to develop a coordinated, across-site, approach to conducting outreach about the study.

Community involvement via a CAP or an alternative participatory mechanism will be crucial in achieving a high participation rate at each site and the sample size requirements of the study. In advance of the start of the study, outreach and engagement will involve announcements to local elected officials, medical societies/community health clinics, local media, community organizations, local unions, the public school system, and local private schools (**Attachment 5**). Outreach may also involve meetings with community representatives, medical societies, school officials, and/or public meetings. Although active in outreach, state and local agencies, CAPs, unions and community organizations will not directly obtain consent, intervene, or interact with research participants. As part of the outreach, the recipient will prepare a factsheet for distribution to state and local agencies, unions, and community groups (**Attachment 5, Attachment 7c**).

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4.2 Recruitment

For sites with a contaminated public water supply, the recipient will request a list of residences served by the water purveyor. The information requested will include the name of the person on the residential account and the street address of the residence. The recipient will also request information from the water purveyor on the distribution system characteristics, in particular, whether the PFAS concentrations can be assumed to be relatively uniform throughout the system or whether the system had specific areas with substantially higher or lower PFAS concentrations. If uniform PFAS concentrations can be assumed, then a random sample of households may be conducted, and recruitment letters mailed to these households. If the system has specific areas with substantially higher PFAS concentrations, then households in these areas will be targeted (oversampled) for recruitment letters.

For sites with contaminated private wells, the recipient will request information on the impacted residences and the results of PFAS sampling of their private wells from the state and/or local health and environmental agencies. Sampling will target households based on the magnitude of the PFAS concentrations in their private wells – i.e., wells with higher concentrations will be oversampled.

Recruitment letters will provide a phone number to call for information about the study and to accept the invitation to participate in the study. The recipient will screen each interested caller using an eligibility screening script (**Attachment 4**). If necessary to achieve a high participation rate and the sampling size goal for the site, study staff may visit the sampled households to recruit participants.

Sampled households may have more than one eligible adult and/or child, and some parents may want to enroll in both of the adult and child studies. Trained study staff will use the recruitment tracking form (**Attachment 6**) to track recruitment success and to calculate non-response bias.

4.3. Enrollment Procedures

Once potential recruits express interest and are screened for eligibility, study staff will schedule appointments for them at the central study office, or alternatively for a home visit for some who are unable or unwilling to attend an office visit and who live a reasonable distance to the office. The study staff will establish a toll-free telephone line for interested recruits to schedule appointments at their convenience. Once the appointment is scheduled, study staff will mail an Appointment Packet (containing an Appointment Reminder Card (**Attachment 7a**), the Informed Consent materials (**Attachment 7b**), a Study Fact Sheet (**Attachment 7c**) with a description to arrive fasting, and to bring medications and a urine sample to the appointment**.** Interested recruits will be mailed urine collection supplies. They will be instructed to collect a first-morning voided urine sample on the day of their appointment. An advance copy of the Informed Consent Form will provide an extra opportunity for the interested recruit to read and more fully understand his or her rights in the study and to ask any questions before the scheduled appointment.

Study staff will give the interested recruit a reminder telephone call and send a text one to two days before the scheduled appointment (**Attachment 8**). The study protocol will provide the flexibility to schedule or re-schedule office or home visits within the study period. Interested recruits who are unable or unwilling to come to the study office and live within a one-hour drive of the study office, will be offered an in-home appointment by trained study staff to complete the study. Interested recruits who request or require a home interview, blood draw, and urine collection, should reside within a one-hour drive from the study office. The study staff will make up to five contact attempts to an interested recruit who misses an appointment in order to reschedule the appointment and maximize the number of completed appointments (**Attachment 9**).

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5.0 Data Collection Procedures

The study will establish a central office in each study site to obtain informed consent, blood and urine specimens, administering the neurobehavioral batteries to parents and children, and providing a space for completion of the questionnaire. Study staff will be available to answer any questions concerning the study. All study staff will receive training on the goals and purposes of informed consent, administration of the questionnaire, administration of the neurobehavioral test batteries, collection methods for the blood specimens, and on proper documentation of data collection procedures. Study staff will receive certified training on Human Subjects Protection (e.g., Collaborative Institutional Training Initiative [CITI] Program) and sign a confidentiality agreement prior to contact with potential recruits and enrolled participants.

Trained study staff will attend dedicated telephone lines to respond to questions and to address concerns from potential recruits, enrolled participants, and the public. Study staff will ask participants to attend their appointment in at least an eight-hour fasting state; therefore, most recruits will likely schedule appointments in the early morning. The steps of the data collection will include:

1. Check-in procedures;
2. Informed consent;
3. Data collection procedures;
4. Exit procedures; including provision of a gift card as a token of appreciation for participation.

5.1 Check-in Procedures

Trained study staff will document the completion of each step from check-in to the provision of gift cards on a hard copy form (**Attachment 9**). This hardcopy form will be stored with the participant's signed Informed Consent Form (**Attachment 7b**) in locked files and in secure rooms. Staff will securely ship all files to ATSDR at the end of data collection. All files and biological samples will be securely stored at the study office prior to shipment.

5.2 Informed Consent Process

The informed consent includes a description of study procedures and risks and benefits of participation (**Attachment 7b**), including a Privacy Act Statement (**Attachment 7b1**). A study factsheet will inform the adult participant and the child participant and parent of the chemical tests and clinical outcomes to be measured (**Attachment 7c**). Study staff will emphasize the voluntary nature of participation and will answer any questions the participant, or parent of the child participant, has prior to obtaining signatures.

5.2.1 Consent for Specimens and Data

The recipient will obtain fasting blood specimens from each participant for analyses of PFAS and several effect biomarkers. In addition, all participants will be asked to provide a morning void urine sample on the same day as their blood draw. After all the current laboratory analyses on blood are completed, the recipient will ask for permission to archive any residual blood specimens and the urines for future analyses of PFAS and/or effect biomarkers.

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If a study participant previously had a PFAS serum measurement, the recipient will ask the participant for the results.

5.2.2 Child Consent

Before any data collection can begin in the child study, trained study staff will review the hardcopy Parental Permission and Assent Form (**Attachment 7b2**) with the parent who is interested in having the child participate. The study staff will explain to the parent and child the purpose of the study and request that the parent sign the permission forms. If the child is seven years of age or older, the study staff will request that the child give an assent to participate in the study.

The recipient will request that the parent complete a questionnaire about the child and complete a parental neurobehavioral test battery on behalf of the child. The permission form will request that the parent allow the child to donate a fasting blood specimen and store any residual specimens for future analyses. The parental permission form will allow the investigators to administer a neurobehavioral test battery to the child, access the child's medical and school records (including special education records) (**Attachments 7b2, 7b3 & 7b5**), and to contact the child and parent for possible future studies. Once the parent signs the consent and permission forms (and the child aged ≥7 years gives assent to participate), the parent and/or the child become study participants in the future.

5.2.3 Adult Consent

Before any data collection can begin in the adult study, trained study staff will review the hardcopy Adult Consent Form with the interested recruit (**Attachment 7b4**). The study staff will explain the purpose of the study and obtain written informed consent for the completion of a questionnaire, the collection of a new fasting blood specimen, the storage of this blood specimen for future analyses, access to medical records (**Attachment 7b5**), and permission to contact the participant in the future for a possible study. After signing the consent form, the adult will become a study participant.

5.2.4 Risks and Benefits

As further described in **Section 3.8.1**, the recipient will inform the participant that his or her participation is protected by a Certificate of Confidentiality under Section 301(d) of the Public Health Service Act as amended by Section 2012 of the 21st Century Cures Act. The recipient will further inform the participant that access to identifiable occupational history, private medical records, and to school records are protected from certain disclosures under Section 301(d) of the PHSA.

The risks of participation in this study are minimal (defined in 45 CFR 46.110). In-home urine collections are minimal risk. This study plans for a one-time 23-ml (5 teaspoons) volume of fasting blood collected from the child and a one-time 33-ml volume of fasting blood collected from the adult. These amounts of blood are the minimum necessary to conduct analyses for PFAS and the effect biomarkers (**Attachment 2**). After the blood draw, the participant will be offered a small snack, thereby allowing monitoring of adverse events due to phlebotomy.

Participants in this study will not receive any direct benefit from taking part in this research. Their taking part in this research will provide the scientific community and the public a better understanding of how exposures to PFAS-contaminated drinking water may affect human health. Each adult participant and the parent of the child participant will receive the results of the analyses of serum PFAS levels and effect biomarkers. They will receive the results of their urine PFAS and effect biomarker levels, if ATSDR identifies meaningful urinary analyses to perform.

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5.2.5 Update Contact Information and Medication List

The adult participant and the parent of the child participant will be asked to verify and update his or her current contact information for results reporting and potential future contact (**Attachment 10**).

The study staff will request that the adult participant and the parent of the child participant bring all current prescription and over the counter medications prior to the study office. This will help the study staff to complete the medications list (**Attachment 11**).

5.3.1. HIPAA Authorization

The Health Insurance Portability and Accountability Act authorization form is a part of the informed consent form and will be reviewed and signed by the study participant in addition to reviewing and signing the informed consent form.

6.0 Exit Procedures

At the end of the data collection, study coordinators or staff will review recorded items in the participant's Appointment Tracking Form for completeness (**Attachment 9**).

The adult participant or the parent of the child participant will receive a copy of the participant's Body and Blood Pressure Measures Report (**Attachment 19**). These results will be immediately available and will require no further evaluation or interpretation with two exceptions. The adult participant or the parent of the child participant will receive a supplemental notice if the participant has a critical blood pressure measure (diastolic blood pressure > 120 mm Hg, or systolic blood pressure >180 mm Hg). In this case, a Critical Hypertension Notice will be appended to the Body and Blood Pressure Measurements Report along with written and verbal recommendations to obtain immediate medical attention. If the participant does not have a personal physician, the study coordinator will provide a referral. If the participant has an elevated but non-critical blood pressure measure (resting blood pressure > 140/90), an Elevated Hypertension Notice will be appended to the Body and Blood Pressure Measures Report with written and verbal recommendations to obtain clinical follow-up.

6.1 Gift Cards as a Token of Appreciation for Participation

As a token of thanks for participation, the recipient will offer gift cards according to the following schedule:

- $25 for body and blood pressure measures, and for blood and urine collection;
- $25 for completed questionnaire; and
- $25 for child/parent completion of the neurobehavioral test battery

Trained study staff will document provision of gift cards on the hard copy form (**Attachment 9**). As part of the exit procedures, the participant will sign this form to document receiving the gift card.

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7.0 Safety Reporting

The risks associated with this study are minimal. There is a small chance of unexpected or adverse events occurring during the course of this project. Unanticipated problems involving risk to the subjects or others will be reported to the CDC Human Institutional Review Board (IRB) in accordance with institutional policies and procedures.

The most likely adverse event is a participant feeling lightheaded or fainting during blood collection. The phlebotomist will receive training to respond to such situations. The tests and procedures conducted by trained study staff are for research purposes only and are not diagnostic exams. They are not a substitute for an evaluation by a medical professional. The study will not perform any clinical treatments or health interventions as part of the study.

If a participant loses consciousness, falls, is unable to stand, or experiences chest pain the study staff will decide whether to advise the adult participant or the parent of the child participant to seek immediate medical treatment or to contact emergency medical services. Study staff have identified appropriate local medical care providers that participants may be referred to if clinical results suggest medical attention is needed.

List medical care providers in the vicinity of the study office (contractor):

- *Definitions of adverse events, serious adverse events and unanticipated problems*
- *Responsibilities of NIA and investigators*
- *Reporting processes*
- *Description of terms used in reporting*

Table. Handling adverse events.

Event	**Action**
Participant feels: Dizziness Nausea Light-headed Weak	Nurse will: Have participant lie down, prop his/her feet up, examine and monitor the participant
Participant: Loses consciousness Falls Is unable to stand	Nurse will: CALL 911 and notify other health personnel in the building.

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Experiences chest pain	

Any adverse event, no matter the severity, will be recorded. The log form for adverse events may be found below.

Name	**Date**	**Time**	**Description of event**	
Name *Address* *Phone*		am/pm		

Unanticipated problems involving risk to the subjects or others will be reported to the CDC Human Institutional Review Boards (IRBs) in accordance with institutional policies and procedures [http://intranet.cdc.gov/od/oads/osi/hrpo/guides/4-incidents-v1.1.pdf

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8.0 Study Compliance

This section describes what constitutes a protocol deviation and process for reporting deviations to appropriate parties, including the site investigator, the DSMB or Safety Officer. Only protocol deviations that impact participant safety should be reported within 24 hours of occurrence if possible, or as soon as they are discovered. All other deviations should be reported routinely to the independent safety monitoring body. Investigators need to follow the CDC IRB requirements for reporting protocol deviations to the Board.

In addition, if ATSDR monitors discover any of these deviations during a site visit, they should list any such occurrence in their monitoring report. The site study coordinator should maintain a log of all protocol deviations.

Protocol deviations/violations may include, but are not limited to, the following:

- Enrollment of an ineligible participant
- Failure to obtain Informed Consent
- Enrollment of a participant into another study
- Wrong questionnaire or neurobehavioral testing administered to participant

A log for recording protocol deviations should also be included in the appendix. See Protocol Deviations Form Template.

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9.0. Body Dimension and Blood Pressure Measurements

Blood pressure, height, and weight may be measured in any order, but the resting blood pressure should be obtained after the subject has been in the seated position for at least five minutes. *It is also desirable for blood pressure to be measured before venipuncture.* Record all measurements on the physical measurement form. Write "refused" for any measurement refused by the participant.

9.1. Height and Weight

Height and weight of participants will be measured and recorded. Determine the BMI using the attached chart.

Material and Equipment

- SECA Stadiometer (Accuu-Hite Measuring Device with Level Bubble)
- Health-O-Meter Physician Beam Scale

Procedure

Before measuring height, check to make sure the floor is level, the wall is at a 90 degree angle to the floor, the wall is straight, and the Stadiometer is mounted perpendicular to the floor. Make sure the participant is barefoot or wearing thin socks.

For accurate measurement of height, the participant must be standing in a vertical plane. To achieve this position, have the participant stand erect on the floor, with back against the vertical Stadiometer, arms hanging freely by the sides, heels against the wall, and feet or knees together—whichever comes together first. Have the participant look straight ahead, with head in the Frankfort horizontal plane. The Frankfort Plan is an imaginary line from the lower margin of the eye socket to the notch above the tragus of the ear (the fleshy cartilage partly extending over the opening of the ear). When aligned correctly, the Frankfort Plane is parallel to the horizontal headboard and perpendicular to the vertical back piece of the Stadiometer.

Ask the participant to inhale deeply. Place the headboard over the crown of the head, with the headboard forming a right angle to the scale. The headboard should touch the scalp lightly.
Ask the participant to step out from under the headboard. Record the height to the nearest 0.5 in on the Physical Measurements Form.
If actual height of participant is unable to be measured because the headboard does not rest directly over the scalp, estimate height to the nearest 0.5 in and record on the Physical Measurement Form. Answer "yes" to the question, "Was there a modification in protocol?"
If participant is wheelchair bound, request estimate of height from participant. Document the height on the Physical Measurement Form and answer "yes" to the question, "Was there a modification in protocol?"

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Before measuring weight, check to make sure scale is on a hard level surface. Step on and off the scale a few times to align all internal parts. Place both poise weights on zero. The beam pointer should float gently up and down and not at the top or bottom of the trig-loop.
Set the large and small poises to indicate the approximate weight. Have the participant stand in the middle of the platform of the scale, with head erect and eyes looking straight ahead. Continue to adjust the small poise until the pointer is centered. It is not necessary to wait for the pointer to stop moving in order to read the correct weight. Add the reading of the small poise to the reading of the large poise for the total weight. Record the results, to the nearest pound, on the Physical Measurements Form.

If the participant is too obese to stand securely on the scale's platform when looking straight ahead, he/she may stand sideways on the scale to take the weight measurement; facing to the side rather than the front will provide the participant a wider base and more stability. If a participant has a prosthetic limb or breast prosthesis, measure weight with the limb on. If participant is frail or unsteady, measure weight while participant is lightly steadied by a member of the office staff. If a participant is unable to stand on the scale for a weight measurement, do not attempt a weight measurement. Answer "yes" to the question on the Physical Measurements Form, "Was there a modification in protocol?"

If the weight of the participant is between 350-400 pounds, use the following guidelines:

- Place the large (lower) poise weight in the 250 lbs. notch (this will weight 350 lbs. with the addition of the 100 lbs. counterweight).
- Hang the counterweight on the lower poise bar in the notch between 100 lbs. and 150 lbs.
- Move the small poise weight along the upper poise bar until the pointer is centered in the trig loop
- To arrive at the participant's total weight, add 350 lbs. to the weight registered by the small poise weight. EXAMPLE: for a client weight 378 lbs., the large poise weight will be on 250 lbs. and the small poise weight on the upper bar will be on 28 lbs.

If the weight of the participant exceeds 400 lbs., use the following guidelines:

- Place the largest (lower) poise weight in the 300 lbs. notch (this will weight 400 lbs. with the addition of the 100 lbs. counterweight).
- Hang the counterweight on the lower poise bar at the notch between 100 lbs. and 150 lbs.
- Move the small poise weight along the upper poise bar until the pointer is centered in the trig loop.
- To arrive at the participant's total weight, add 400 lbs. to the weight registered by the small poise weight.

9.2 Blood Pressure

Blood pressure (BP) level is a major risk factor for coronary heart disease, congestive heart failure, and stroke. Heart rate reflects autonomic nervous system function and cardiovascular fitness. The measured BP level is subject to biological and observer variability. The purpose of a specific measurement protocol, or training and certifications of technicians and of ongoing quality control is to minimize variability due to known exogenous factors and to reduce imprecision and biases in measurement.

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Materials and Equipment

- Blood pressure cuffs in four sizes (or automatic)
- Stethoscope
- Measuring tape (for arm circumference)
- Watch or stop watch (to time five-minute rest and resting heart rate).
- Copy of chart for choosing correct BP cuff sizes
- *Information sheet on interpretation of BP from JNC*
- Physical Measurements Form
- Referral Form

Procedure

The participant should be seated and relaxed in a comfortable chair. Record the date of the procedure on the physical measurements form during the five minute rest period, and make sure that the room temperature is between 70 and 76 degrees Fahrenheit. The surroundings should be free of excessive noise or distractions. Before the BP measurement procedure, explain to the participant what to expect and how long the procedure will take. The following script is suggested:

> "This part of the visit involves taking your resting blood pressure. It will take about 10 minutes. We would like you to sit with both feet on the floor and your arm supported on the table. We will have you sit quietly for five minutes. Then we will take your blood pressure three times, two minutes apart. We will tell you your blood pressure readings and give you some material to help you interpret them at the end of the session."

Use the proper cuff size to avoid under- or over-estimation of the correct blood pressure. Selection of the proper sized cuff is based on the guideline that the length of the inflatable bladder in the cuff should be at least 40% of the arm circumference. If necessary, measure the right arm circumference as follows:

- Ask the participant to bare the upper arm.
- Instruct the participant to sit or stand holding forearm horizontal, i.e., parallel to the floor.
- Measure arm length from the acromion (bony extremity of the shoulder girdle) to the olecranon (tip of the elbow) using a metric tape.
- Mark the midpoint on the dorsal (back) surface of the arm.
- Ask the participant to relax arm along the side of the body.
- Draw the measuring tape snugly around the arm at the midpoint mark, keeping the tape horizontal. Tape should not indent the skin.
- Use the following chart to determine appropriate cuff size (Chart adapted from the Human Blood Pressure Determination by Sphygmomanometry by the American Heart Association).

Arm Circumference (cm)	**Cuff Name**
17-21.9	Child/Small Adult
22-29.9	Adult
30-37.9	Large Adult

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38-47.9 Thigh

The participant should not talk, eat, or drink during the procedure, as these activities will actually elevate blood pressure readings. Both feet should be on the floor and the forearm should rest on a table or other support. The subject should sit up, not slouch.

After the resting period, place the appropriate cuff around the upper right arm so that the mid-height of the cuff is at heart level. Palpate the patient's brachial artery and place cuff so that artery is aligned with the cuff arrow marked "artery". Place the lower edge of the cuff, with its tubing connections, two centimeters above the natural crease across the inner aspect of the elbow. Wrap the cuff snugly around the arm, with the palm of the participant's hand turned upward. Secure the wrapped cuff firmly by applying pressure to the locking fabric fastener over the area where it is applied to the cuff. Do not wrap the cuff too tightly around the arm.

Occasionally there will be a participant whose upper arm is too thick and short for the thigh cuff or on whom the thigh cuff pops open on inflation. The alternative procedure in this case is to obtain the resting blood pressure in the right forearm as follows:

- Measure the forearm circumference at midpoint between the olecranon and the ulnar stylus (wrist bone on the pinkie side).
- Select the proper size cuff based on the forearm measurement.
- The blood pressure procedure is the same otherwise.
- Document on the Physical Measurements Form

Record the three readings on the physical measurements form. Determine appropriate actions for elevated blood pressures based on the guidelines below and inform the participant of the recommended action.

Referrals

If a referral is required (BP > 140/90 on at least 2 readings), note the participant's BP on a referral form, and give the marked form to the participant. If the participant does not have a healthcare provider, the office staff will provide a referral to [list names of clinics]. The organization of referral should be noted on the Physical Measurements Form.

It is up to the participant to share or not to share the abnormal results shared with his/her healthcare provider. Study stuff may advise participant but is not responsible for making him/her to share the data.

Participants with abnormal blood pressure readings on at least two of the three readings will be referred to a healthcare provider according to the following guidelines:

This chart reflects blood pressure categories defined by the American Heart Association.

Check One	BP Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)	Action*
	Normal	<120	AND	<80	Your blood pressure is normal. You

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					should still continue to have your regular appointments and check-ups with you doctor
	Elevated	120-129	OR	<80	Your blood pressure is slightly above normal. You should still continue to have your regular appointments and check-ups with you doctor.
	Hypertension (Stage 1)	130-139	OR	80-89	Your blood pressure is very high. You should call your doctor and ask for an appointment. Please take this form with you and show it to your doctor. If you do not have a doctor, we will help to find you one.
	Hypertension (Stage 2)	≥ 140	OR	≥ 90	Your blood pressure is very high. You should call your doctor and ask for an appointment. Please take this form with you and show it to your doctor. If you do not have a doctor, we will help to find you one.
	Hypertensive Crisis	≥180	AND	≥120	Your blood pressure is dangerously high. You cannot continue with the study. You should call you doctor right now and ask to be seen as soon as possible. Your doctor may want you to go to the emergency room instead of waiting for an appointment. Please take this form with you and show it to your doctor. If you do not have a doctor, we will help to find you one.

Blood pressure categories

The five blood pressure ranges as recognized by the American Heart Association are:

Normal

Blood pressure numbers of less than 120/80 mm Hg are considered within the normal range. If your results fall into this category, stick with heart-healthy habits like following a balanced diet and getting regular exercise.

Elevated

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Elevated blood pressure is when readings consistently range from 120-129 systolic and less than 80 mm Hg diastolic. People with elevated blood pressure are likely to develop high blood pressure unless steps are taken to control the condition.

Hypertension Stage 1

Hypertension Stage 1 is when blood pressure consistently ranges from 130-139 systolic or 80-89 mm Hg diastolic. At this stage of high blood pressure, doctors are likely to prescribe lifestyle changes and may consider adding blood pressure medication based on your risk of atherosclerotic cardiovascular disease (ASCVD), such as heart attack or stroke.

Learn more about your risk with our Check. Change. Control. Calculator™.

Hypertension Stage 2

Hypertension Stage 2 is when blood pressure consistently ranges at 140/90 mm Hg or higher. At this stage of high blood pressure, doctors are likely to prescribe a combination of blood pressure medications and lifestyle changes.

Hypertensive crisis

This stage of high blood pressure requires medical attention. If your blood pressure readings suddenly exceed 180/120 mm Hg, wait five minutes and then test your blood pressure again. If your readings are still unusually high, contact your doctor immediately. You could be experiencing a hypertensive crisis.

If your blood pressure is higher than 180/120 mm Hg and you are experiencing signs of possible organ damage such as chest pain, shortness of breath, back pain, numbness/weakness, change in vision or difficulty speaking, do not wait to see if your pressure comes down on its own. Call 911

Classification of BP in Adults Aged 18 Years or Older.
* If systolic and diastolic categories are different, the shorter recommended time for recheck and referral takes precedence. If two or three repeated systolic or diastolic measurements are abnormal but fall in different categories, determine the appropriate category based on their average.

If two or three repeated systolic or diastolic measurements are abnormal but fall in different categories, determine the appropriate category based on their average.

All elevated blood pressures will be recorded on the Participants Body and Blood Pressure Report.

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10.0. Blood Sample Collection, Processing and Shipping Protocol

Venipuncture should be performed in the fasting state after the blood pressure measurements. In adults, **40 ml** of blood shall be collected to recover about 14 ml of sera for the analyses of PFAS and clinical and other effects biomarkers, as well as 3ml of whole blood for the analyses of glycated hemoglobin and whole blood reserve. In children, **30 ml** of blood shall be collected to cover 2 ml of whole blood and about 11 ml of serum for PFAS and clinical and other effects biomarkers (See Attachment 3 for details).

The volumes to be collected have been adjusted following the discussions with commercial laboratory to be selected for the analyses of clinical and other effects biomarkers.

The study office will need to have appropriate space designated for blood processing where whole blood and serum aliquots can be accomplished.
The ATSDR, contractor, and commercial laboratory will determine whether conditions on site are appropriate to accomplish this task.

***NOTE**: Universal Precautions should be adhered to as defined in the OSHA Blood-borne Pathogens Standard (29 CFR 1910.1030).*

10.1. Blood Collection Procedure

Have the following items on hand and available for use. Blood collection and processing supplies will be provided by CDC as indicated. Contractor provided supplies/equipment are also listed below.

CDC provides:

- Disposable gloves
- Tourniquet
- Alcohol disinfectant swabs
- Gauze pads
- 21g butterfly needle or 21g Vacutainer straight needle (smaller 23 g needle may be required for difficult collection)
- Tube needle holder
- Four 10 ml red top tubes (NO Serum Separator Tubes) for **Serum**
- One 3 ml EDTA purple top tube for whole blood
- Adhesive bandage
- Sharps disposal container for used needles
- Serum tube rack
- **All labels**

***Contractor** provides:*

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- Refrigerator and -70°C freezer for storage of serum and blood samples
- Smelling salts
- Electrolyte drink
- Basin
- Cold wet cloth

Blood collection procedure guidelines:

1. Tie the tourniquet onto the upper arm so that it can be quickly released with one hand.
2. Swab the venipuncture area with alcohol pad.
3. Allow to air dry for 5 - 10 seconds.
4. Using standard venipuncture procedures puncture the vein.
5. After blood flow is established, loosen the tourniquet.
6. **Collect four (three for children) red top serum tubes [(10 ml in first three tubes (two for children) and 8 ml in the fourth (third for children)**
   (Please note: If the child is 8 years old or younger or those who weigh less than 60 pounds use six (6) 5 ml red top collection tubes)
7. Push purple top tube into the needle holder.
8. **Collect two EDTA purple top tubes (1 ml each)**
9. Mix well (EDTA 8-10 inversions) after collection or place in a tube rocker.
10. Allow the vacutainer red top tubes to fill.
11. Red tops should be allowed to clot upright in a rack (for at least 30 min but no more than 2 hours.)
12. Withdraw the needle and dispose of in the sharps disposal container.
13. Apply pressure on the venipuncture site and apply a bandage.
14. Place labels on blood tube vial so that when the tubes are upright, the barcode looks like a ladder. Record the sample collection using the label for "Log". Note any problems with the collection, i.e., low volume, could not collect, etc.

For those participants who are extremely apprehensive about giving blood, follow the guidelines below:

- Explain to the participant that the blood draw is designed to be as painless as possible. It may help to let the participant go on with another part of the visit and return later for the blood draw. Do not, under any circumstances, force the participant to have blood drawn.
- If the blood sample is not forthcoming, the following manipulations may be helpful:
  - If there is a sucking sound, turn needle slightly or lift the holder in an effort to move the bevel away from the wall of the vein.
  - If no blood appears, move needle slightly in hope of entering vein. Do not probe. If not successful, release the tourniquet and remove needle. A second attempt can be made on the other arm.
  - Loosen the tourniquet. It may have been applied to tightly, thereby stopping the blood flow. Reapply the tourniquet loosely. Be sure, however, that the tourniquet remains on for no longer than two minutes at a time.
  - Do not attempt venipuncture more than three times.
  - Reassure the participants that your inability to obtain a clean venipuncture is not any sign of a medical problem on their part.

- If venipuncture is unsuccessful, note on the Physical Measurements Form.

- If the participant looks or feels faint, follow the guidelines below:
  - Have the participant remain in the chair and sit, if necessary, with head between knees until his/her color returns and he/she feels better.
  - Provide a basin if the participant feels nauseated.
  - Place a cold wet cloth on the back of the neck.
  - If the participant faints, use smelling salts to revive by crushing the ampoule and waving it under the nose for a few seconds.
  - If the person continues to feel ill, contact a medical staff member for advice.
- If it is not possible to fill all tubes (e.g., blood flow ceases, difficult venipuncture, etc.), make a note of the departure from protocol on the Physical Measurements Form. If the participant is willing, a second attempt can be made to complete the blood draw.

Whole Blood Processing Table:

Analyte	Amount Needed	Storage Container	Storage Temp	Shipping Info
Blood HbA1c	1.0 mL whole blood	3.0mL EDTA Purple-top Vacutainer	Freeze at -20°C	Ship to Commercial Lab
Reserve	1.0 mL whole blood	3.0mL EDTA Purple-top Vacutainer	Freeze at -20°C	Ship to CDC

After blood draw is completed, the study participant may be shown to the snack area. Snacks and beverages should be available to all participants after completing the blood draw. Diabetic participants should be advised to eat and take any necessary medications at that time.

10.2. Serum Processing Procedure

1. Materials and Equipment Needed per Participant
   - Disposable gloves (CDC)
   - Disposable plastic pipets (CDC)
   - 50 mL centrifuge tube **SERUM (CDC)**
   - **Three (3) 2 mL cryovials (CDC)**
   - **Six (6) 12 ml vials for shipping to commercial lab (Contractor)**
   - Bar-coded labels CDC
   - Two centrifuges (CDC)
   - Freezer **(Contractor)**
2. Processing

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- After the blood has been allowed to clot at room temperature for a minimum of 30 minutes (2 hours is preferred), centrifuge the red-top tubes for 15 minutes at 2400 rpm.
- To maximize the amount of serum recovered from all of the red top tubes after centrifugation, do the following:
    a. Using a disposable pipet, transfer all of the clear serum that is free of red cells from each red top tube collected from a participant to one of the 50 ml centrifuge tube.
    b. If less than approximately 2.0 mL of viable serum was able to be pipetted it is highly recommended that the red top tube completes an additional centrifuging round to obtain additional serum. Centrifuge this red top tube containing the red cell/serum mix for 10 minutes and transfer the clear serum to the 50 ml centrifuge containing the clear serum initially harvested. There should be 3-5 mls of serum from each red top when completed. Place a label for **SERUM** on the centrifuge tube. The label should be placed on the tube so that when the tubes are upright, the barcode looks like a ladder.
    c. *Tighten the cap on the centrifuge tube and store in a freezer until ready to ship to CDC;*
    d. *All cryovials for clinical and effect biomarkers will be shipped to commercial laboratory (See Table below).*
    e. *Aliquots for PFAS analyses will be shipped to CDC.*
    f. *Any excess serum should be aliquoted to additional cryovials provided by CDC in 1 ml aliquots, labeled and shipped to CDC on dry ice.*

Serum processing table (aliquots needed for clinical and effects biomarkers analyses).

Aliquot Number	Analyte	Amount to be aliquoted	Children	Adults	Shipping Info
1-2	**PFAS**	**2 x 1 ml serum**	**Yes**	**Yes**	**CDC**
3	Lipids	0.5 ml serum	Yes	Yes	Commercial Lab
4	Uric acid/Creatinine	1.0 ml serum	Yes	Yes	Commercial Lab
5	Thyroid hormones	0.5 ml serum	Yes	Yes	Commercial Lab
6	Sex hormones	1.0 ml serum	Yes	Yes	Commercial Lab
	Liver tests				
7	Standard	0.5 ml serum	Yes	Yes	Commercial Lab

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8	CK-18 (M60, M35)	1.0 ml serum	Yes	Yes	Commercial Lab
9	Immune function (Immunoglobulins, Cytokines))	3.0 ml serum	Yes	Yes	Commercial Lab
	Glycemic parameters				
10	…Glucose/Insulin	0.5 ml serum	Yes	Yes	Commercial Lab
11	…Antibodies (IA2, GAD 65)	1.0 ml serum	Yes	Yes	Commercial Lab
12	Vaccines Antibodies	1.0 ml serum	Yes	Yes	Commercial Lab
13	Autoimmune parameters	2.0 ml serum	No	Yes	Commercial Lab
14	Inflammatory cytokines	1.0 ml serum	No	Yes	Commercial Lab
	[Total Serum needed for planned clinical and effect biomarkers analyses]		11 ml	14 ml	

10.3. Collection Log

A collection log is provided or an electronic spreadsheet may be created to record samples that are collected. Please mark the appropriate spaces on the manual log or record electronically, indicating which aliquots were collected, date collected and any problems that were encountered in collection, storage, or shipping.

Collection log template.

DLS Study number **DLS study Name** **SAMPLE COLLECTION LOG SHEET**	
SHIPMENT DATE:_____	RECEIPT DATE:_____
SHIPPED BY:_____	RECEIVED BY:_____

UC= Urine Cup, RT= Red top (blood tube for serum yield)

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Place a label in the label section of the specimen log sheet.

☒ = SPECIMEN COLLECTED ☐ = SPECIMEN NOT COLLECTED (Please leave blank if specimen is not collected)

LABEL			Comments:	LABEL			Comments:
	UC				UC		
	RT				RT		
LABEL			Comments:	LABEL			Comments:
	UC				UC		
	RT				RT		
LABEL			Comments:	LABEL			Comments:
					UC		
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					UC		
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LABEL			Comments:	LABEL			Comments:
	UC				UC		
	RT				RT		

10.4. Shipping instructions for serum and whole blood specimens

There are storage boxes provided for each container type. These should be used for storage of samples in the freezer or refrigerator and when samples are shipped to CDC or commercial laboratory.

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1. Materials and Equipment Needed (when needed to be provided by contractor noted):
   - Biohazard plastic bags large enough for individual specimen storage boxes to be placed inside
   - Absorbent pads or other absorbent material
   - Filled specimen storage boxes containing serum vials
   - Styrofoam shipping containers with outer cardboard liner
   - Dry ice (for Serum) **(contractor)**
   - Dry ice label (for Serum)
   - Ice packs (freeze before using) for shipping purple top tubes
   - Diagnostic Specimen label (for all shipments)
   - Completed FedEx air bill **(contractor)**
   - Packing material (bubble wrap or newspaper) (**contractor)**
   - Packing tape **(contractor)**

2. Packing Instructions (serum):
   - All specimens should be placed in an appropriate sized gridded storage box. Place the specimen storage boxes inside one of-biohazard bags along with an absorbent pad s and seal the bag.
   - Wrap 1 rubber band horizontally along the Specimen box and 1 rubber band vertically. This will create a (+) design on top and ensures the box stays closed during shipping

   - Place an absorbent underneath the overlapping rubber bands on top of the specimen boxes

   - Place specimen filled storage boxes inside biohazard bag and seal bag securely shut

   - Place bagged specimen boxes inside Styrofoam shipper neatly so that the samples will likely remain in an upright position as they travel. Add 10-15 lbs. of dry ice to keep the samples

frozen during transportation. Add extra packing material around the specimens (newspaper, paper towels, bubble wrap, etc.).



- Prepare a Federal Express air bill for shipping and mark the appropriate boxes including the one for dry ice for the Serum shipment and overnight delivery.
- Place a Dry Ice Label and a Diagnostic Specimen Label on the outside of the shipping box containing the Serum Specimens and write in the weight of the dry ice.

3. Packing instruction whole blood (purple top tubes)
   - Wrap 1 rubber band horizontally along the Specimen box and 1 rubber band vertically. This will create a (+) design on top and ensures the box stays closed during shipping

   - Place an absorbent underneath the overlapping rubber bands on top of the specimen boxes

   - Place specimen filled storage boxes inside biohazard bag and seal bag securely shut

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- Place bagged specimen boxes inside Styrofoam shipper neatly so that the samples will likely remain in an upright position as they travel. Add frozen cold pack to keep the samples refrigerated during transportation.

- Add additional packing material to insure that the sample boxes will be secure in the box and will not be moving around.
- Place the Styrofoam lid on the box.
- Close the outer cardboard flaps and tape using either nylon reinforced filament tape or heavy duty packing tape Scotch Premium Heavy Duty 3750-RD Packaging Tape.
- Be sure to include a paper manifest documenting the samples being sent.
- Package is to be sent Priority Overnight; Ship only Monday-Wednesday, NOT over Weekend or Federal Holiday.
- Send an email to Sample Logistics (ncehsamplelogistics@cdc.gov / wvg4@cdc.gov) and the CDC coordinating staff member to inform them of the package's expected arrival date and attach an electronic copy of the manifest.

The electronic manifest should include the following information: Specimen ID, any local ID (additional ID in the vial, if applicable), sample matrix, Box#, Position within the box, sample volume, collection date-if available, analytes to be measured, any other pertinent comment. Specimen ID.

Specimen ID	Local ID (if any)	Matrix	Box #	Position in Box	Volume (mL)	Collection Date	**Analytes to be measured**	Any pertinent comments
							Choose an item.	

-
(For PFAS serum ONLY)

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4. CDC Warehouse
3719 N Peachtree Road
Chamblee, GA 30341
ATTN: Sample Logistics- Sina De Leon Salazar
Chamblee Building 109, Room 1312B
TEL: 770-488-7227/ FAX: 770-488-4301
EMAIL: NCEHSampleLogistics@cdc.gov / wvg4@cdc.gov

CDC Biorepository
602 Webb Gin House Rd., Bldg. C
Lawrenceville, GA 30045
-ATTN: **Rob Davidson** (440-339-5942, mobile)
Back up contact: Julie Chatt 404-263-5806 (mobile)

EMAIL: biorepository@cdc.gov

Please-email the information about the shipment to the emails provided in the Sample Logistics shipping address (NCEHSampleLogistics@cdc.gov and wvg4@cdc.gov) the day that the package is shipped. Shipments should be made on Monday through Thursday to insure that the shipment will arrive during a regular work day.

Collected serum will be aliquoted and shipped by the contractor to laboratories in volumes required as detailed in Attachment 3 of the Protocol for clinical biomarkers analyses.

For the reserve samples:
The whole blood reserve aliquot, reserve serum aliquots, and urine collection cup (see section 10.5) will be assigned and labeled with CDUID and shipped to CDC biorepository facility for storage. The contact person for the CD biorepository is:

Marcy Revelez
Acting Team Lead and Collections Manager, CDC Biorepository
Informatics and Data Science Branch
Division of Laboratory Systems
Center for Surveillance, Epidemiology, and Laboratory Services
U.S. Centers for Disease Control and Prevention
Office: 404-498-1665; CDC Mobile 404-797-1318
CDC Biorepository Intranet Site: https://esp.cdc.gov/sites/csels/DLS/biorepository/default.aspx

10.5. Urine Collection Instructions

All participants will be mailed a labeled urine collection cup, urine collection instructions (see Steps below), gloves, insulated cooler, and ice pack, which they'll be instructed to store in their freezer.

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The morning of their blood sampling appointment, participants will collect a first-morning urine sample (filling at least one quarter of the 125 ml collection cup, if possible), cap the container, seal the container in a plastic bag, and place in a refrigerator until they travel to the blood sampling location. Participants will transport their sample to EA staff in an insulated cooler with the frozen ice pack.

When you receive the urine collection kit, please put the freezer pack in the freezer so you can use it to transport your sample to the collection location. Please collect a sample of your first morning urine void on the day of your scheduled blood collection appointment. Write down the date and time of the collection. Please use the following instructions:

> **Step 1:** When you get up in the morning, collect a sample of your urine in the provided cup the first time you use the bathroom. Please try to fill at least one quarter of the cup.
> - Make sure to wash your hands with **water only** before collecting your sample. Do not use any soap, lotion, or other personal care products.
>
> - Put on the provided gloves before collecting your sample.
>
> **Step 2:** Cap the urine collection cup and seal in the provided plastic bag.
>
> **Step 3:** Record the date and time of your collected urinary sample on your urine collection log.
> - If some of the sample spills, or you forget to record the time of collection your sample will still be able to be used for the investigations. Please write down any comments you want us to know about on your collection log.
>
> **Step 4:** Place your sample in your refrigerator until it is time to go to your blood collection appointment.
>
> **Step 5:** Bring your urine sample, inside the provided cooler box packed with the frozen ice pack, and your urine collection log to your blood collection appointment.

The morning of their blood sampling appointment, participants will collect a first-morning urine sample (filling at least one quarter of the cup, if possible), cap the container, seal the container in a plastic bag, and place in a refrigerator until they travel to the blood sampling location. Participants will transport their sample to EA staff in an insulated cooler with the frozen ice pack.

Study staff and NCEH/ATSDR personnel will maintain and manage proper chain of custody for all urine samples.

Collected cups will be placed inside freezer/storage boxes.–Each box will be placed inside a plastic biohazard bag along with an absorbent pad and sealed. The bagged specimen boxes will be placed inside a Styrofoam shipping container. Dry ice will be added to the shipper and urine specimens will maintained in their frozen state. Multi-site study personnel will perform twice daily checks to ensure that samples remain frozen and will add dry ice as needed. All urine samples will be shipped overnight

on dry ice to CDC on Thursdays and Mondays during the sample collection period. Field and bio-specimen repository staff will maintain and manage proper chain of custody for all urine samples.

To protect anonymity, the samples will be labeled with a coded identification number. The identification number on the urine sample will match the identification number on the serum sample in order to pair each individual's blood and urine samples.

Urine samples will be stored CDC biorepository (see section 10.4) as needed for future PFAS analyses.

When the analyses are completed, the PFAS test results will be reported as nanograms per milliliter of urine (ng/mL). Creatinine results will be reported as milligrams per deciliter of urine (mg/dL). Laboratory processing, analysis methods, quality assurance and quality control measures will be conducted in accordance with NCEH laboratory methods.

10.5.1. Study participant urine collection instructions.

URINE COLLECTION INSTRUCTIONS

Please READ CAREFULLY:

- Enclosed is a **plastic cup** and a **plastic bag** with an **absorbent pad inside**.
- DO NOT take the cap off the cup until you are about to collect your urine.
- We would like you to collect your first morning urine, if possible
- Make sure you fill out all the items on the plastic cup label before you put your urine in the freezer.

Instructions for collecting your urine:

- Wash your hands with soap and water.
- Rinse and dry your hands with a clean towel.
- Keep the **cup closed** until you are ready to collect your urine.
- **DO NOT TOUCH** the inside of the cup or cap.
- Open the cup and leave the cap turned up.
- **Collect 30-40 mL of urine.**
- **Do NOT overfill the urine cup.**
- Put the cap back on the filled container and tighten it.
- Wash your hands with soap and water again.
- Fill out the label on the plastic cup as follows:
    - Date
    - Time of urine collection
    - First Morning Urine? Yes or No
    - Time urine put into freezer
- **Put the closed cup filled with urine on the absorbent pad in the plastic bag we gave you,**
- **SEAL the BAG**,
- Put the sealed plastic bag with the filled urine cup in the **FREEZER.**
- **Bring the CUP of FROZEN URINE in the sealed plastic bag to your scheduled blood draw appointment.**

Thanks!

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11.0. Interviewer methods

11.1. Interviewer Certification

All interviewers must be certified to conduct the survey. The certification procedure includes the following training:

A. HIPAA Form
B. IRB Certification
C. Confidentiality Statement
D. Completed Initial Training
E. Interviewer Training:
1. Knowledge of Survey Material
2. Contact Sheet
3. Attempt Documentation
4. Introduction of Survey to Respondent
5. Consent Form
6. FAQ Review
7. Selection of Prior Respondent or Suitable Proxy
8. Reading Techniques
9. Read Questions as Written
10. Speech/Clarity
11. Pronunciation
12. Neutral Probing Techniques
13. Knowledge of Disposition Codes
14. Recording of Answers
15. Practice Interview Scenarios
16. Interview Supervisor
17. Results to Health Care Provider
18. Human Subject Protection

Interviewers must demonstrate competency in all areas to be certified.

11.2. Interviewer Checklist

Aim for a professional look, simplicity, and comfort. The respondent should focus on the interview and not the interviewer's manner of dress.

1. Be prepared to conduct the survey.

2. Survey Materials: a. Identification Badge

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b. Bag
c. CDC laptop, Charged
d. Black Ink Pen
e. Copy of the Pre-Contact Letter sent to Respondent
f. Map & Address Listings (special needs cases)
g. Interviewer Checklist
h. Participant Response Card
h. Contact Tracking Information Form
i. Consent & HIPAA form – digital iPad application and backup paper forms
j. Questionnaire – loaded on laptop and backup paper copies
k. Gift Cards – one each for interview and blood draw
l. Appointment Form-Respondent's Copy
m. Non-participant Form

11.3. Consent Form

As part of the CDC Institutional Review Board for Human Use requirements, all surveys require a consent form before interviewing begins. The consent form tells the participants about the study and their rights as a research participant. The interviewer should read through the consent form with the participant. The participant should initial all required pages of the consent form and sign and date the signature page(s). Two copies of the form are needed: one for the participant to keep and the other for the interviewer to return along with the completed survey.

1. Explain the Consent Form:
   - Summarize topic areas in the Informed Consent Packet
   - Read specimen storage section
   - Read parental permission and child assent information
   - Summarize HIPAA form
   - Leave one copy with respondent
   - Return one copy to field coordinator
2. Make sure that all appropriate pages are initialed by the respondent.
3. Make sure the adult respondent signs and dates the Adult Consent Form (p. 18-19)
4. Make sure the parent and child (if older than 7) sign and date the Parental Permission and Child Assent Form (p. 10-11)
5. Make sure the parent/guardian sings Parental Consent to release student information (p. 12)
6. Make sure respondent also signs and dates the Parent/Child/Adult Medical Record Abstraction form (p.20)

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7. Be sure you have the signed Consent and Authorization Forms in your possession.

Note: The CDC IRB also requires training in human subjects' protection. To fulfill this requirement, all interviewers will watch a video detailing the need for human subject protection or have completed other approved training. Persons who have not reviewed the video or have not completed other IRB approved training will NOT be allowed to conduct an interview.

11.4A. Conducting the Interview: Location

All interviews, with the exception of special needs cases, will be conducted on-site in study office at Portsmouth, NH. Exact site is to be determined by the contractor in consultation with ATSDR. There are additional instructions (Section 4D) for interviews conducted off-site.

11.4B Conducting the Interview: Documentation

1. Type the ID number from the Contact Sheet on first page of Questionnaire.

2. Ask ALL questions as appropriate.

11.4C Conducting the Interview: Asking the Questions

1. Guidelines for Asking Questions

Use the questionnaire conversationally. The interview should be done in an informal and relaxed atmosphere. Interviewers should avoid creating the impression that the interview is a quiz or cross examination. Interviewers must be careful that nothing in their words or manners implies criticism, surprise, approval, or disapproval.

Interviewers should know the questions so that each one can be read smoothly and transitions between questions are made without hesitation. This is possible only when the interviewer has studied the questionnaire carefully and practiced asking the questions aloud in practice interviews.

Ask each question exactly as worded in the questionnaire. Since exactly the same questions must be asked of each respondent, the interviewer should make no changes in the phrasing of

the questions. Not only are deliberate word changes to be avoided, but the interviewer must guard against accidental word changes as well.

Ask the questions in the order presented in the questionnaire. Question order needs to be the same from respondent to respondent if the interviews are to be comparable. Thus, the interviewer needs to stick strictly to the given order.

Ask every question specified in the questionnaire. In answering one question, a respondent will sometimes also answer another question appearing later in the interview. Do not skip the questions even though they may seem to have already been answered or seem repetitive unless there is a skip pattern instruction.

Transitional statements help to conclude one topic and introduce another on a questionnaire. These transition statements aid the interviewer in making the interview seem conversational. Whenever such statements appear in the questionnaire, they should be used. A respondent who has been introduced to a new topic tends to organize his or her thinking more quickly and may well answer the next few questions differently from a respondent who is still involved in thinking about the last topic. Always be sure to read the transitional statements exactly as they are written.

Repeat and clarify questions which are misinterpreted or misunderstood. Questions are phrased to be understood by respondents across the state and you will find that most of the people you interview do understand them. Occasionally, when a respondent does misunderstand or misinterprets something, you should repeat the question just as it is written in the questionnaire. If you suspect that the respondent merely needs time to think it over, simply wait and don't press for an immediate answer. If you think the respondent needs reassuring, you may want to add to the question a neutral conversational remark such as "We're just trying to get people's ideas on this," or "There are no right or wrong answers, we're just interested in your opinions."

Probe for meaningful answers. Sometimes it may be necessary to clarify a respondent's answer. Some questions may seem difficult, or concern matters that the participant doesn't usually think about, and careful probing may be required in order to arrive at meaningful answers.

Probing should always be done in a neutral manner. Your probing questions should be worded in such a way that they do not lead the participant to any particular answer. Acceptable probes include the following.

a. A brief assertion of understanding and interest.
b. An expectant pause.
c. Repeating the question or response options.

d. Repeating the respondent's reply.
e. Providing a neutral question or comment.
f. Asking for further clarification.
g. "What do you mean?"
h. "Tell me more about what you have in mind."
i. "What do you think?"
j. "Which answer would be closer?"
k. "Are there any others?"

Clarification for the respondent should be done if there is any doubt that the respondent did not understand or hear the question or response options. Repeat the question if needed. Repeat all response options if asked to repeat one or more of them. Do not provide definitions of words or questions. Instead, state "I am not allowed to provide definitions for words or questions, so please use whatever _____ means to you."

It is important to give feedback to respondents to let them know that you are listening, to keep them motivated, and to encourage further response. However, this feedback should be neutral and show any approval or disapproval towards the respondent. Acceptable feedback phrases include the following.

Short	I see. Uh-huh. Thanks.
Long	That's useful / helpful information. It's useful to get your ideas on this. Thanks, it's important to get your opinions on that. I see; that's helpful to know. It's important to find out what people think about this. That's useful for our research.
Task-related	Let me get that down. I need to write all of this down. I want to make sure I have that right… (repeat answer) We have touched on this before, but I need to ask every question in the order that it appears in the questionnaire so… (ask question).

2. Closed-ended Questions

Most of the questions in the study have a set of pre-coded answers. In order to record the participant's answers to the questions, the interviewer must circle the code number of the answer given. This is the most common type of question.

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Example:

A5. What race do you consider your child to be? Mark all that apply.
___American Indian or Alaska Native
___Asian
___Black or African American
___Native Hawaiian or Other Pacific Islander
___White
___Refused to answer

If the respondent had answered that he or she considered their child to be “White” the interviewer would put a check mark next to the “White” response.

3. Other-specify Questions

Some questions have an “other-specify” option. In these cases, if a respondent provides an answer that is not part of a pre-coded list, the interviewer will write the answer exactly as the participant says.

Example:

A1. What is your relationship to your child?
___Birth mother
___Birth father
___Adoptive mother
___Adoptive father
___Legal guardian
___Other relationship: specify _____
___Refused to answer

If a respondent gives an answer that does not appear on the list provided, the interviewer should write it clearly and completely on the line next to “other.” Print all responses in the participant’s exact words. Do not correct people’s grammar or substitute you own words – we want to know what people say.

4. Numeric-response Questions

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Some questions require writing a number in the blanks provided in the response set. If there are two spaces, you need to fill in two numbers. If the person says "6" then write "06." If the person gives a range of numbers for a response then you should probe for clarification. For example, if the respondent has answered "Uh…5, 6, or 7, I guess…" say "I can put down 5, 6, or 7, which one would like me write down."

Example of Number:

A3. What is your child's age? ___(YY) ___Refused to answer

Example of Frequency:

B2. On average, how many 8 oz. cups of tap water or beverages prepared with tap water does your child currently drink per day at home? ___ cups ___Doesn't drink tap water ___Don't know ___Refused to answer <u>Note: 1 cup = 8 oz.; 2 cups = 1 pint (16 oz.); 4 cups = 1 quart (32 oz.); 16 cups = 1 Gallon (128 oz.)</u>

In these cases, a participant's answer may be given in terms of cups, pints, quarts, or gallons. The interviewer must convert the given liquid measure into the appropriate amount of cups per day and fill in the space beside it. For example, if someone responded with "4 cups a day" the interviewer would write "04" in the blanks next to the "cups" response. This format allows answers to be recorded easily and precisely. If the respondent answers that their child does not drink tap water, then the interviewer would mark next to the "Doesn't drink tap water" response and leave the "cups" response blank.

Again, if the respondent answers with a range of numbers, you should probe for clarification.

<u>5. Open-ended Questions</u>

This type of question has no pre-coded responses at all, but simply asks you to write what the person says. It is important that you write what they say without adding or changing words.

Example:

E1. Have you ever been told by a doctor or other health care provider that your child has or had any of the following medical conditions? Fill out the table below. Circle appropriate response and ask the respondent to specify as directed.

____ q. How is your child treated for their learning or behavioral problems?

6. Gathering Personal Data

Questions about the respondent's age, marital status, and income are toward the middle of the questionnaire. You can usually ask these questions with no resistance on the part of the respondent. However, if the respondent asks why you want personal data, reassure the respondent that all of the information gathered will be combined and their individual answer will not be reported and that the information is used only to see if different groups of people are similar or different in their health. You may also add that the interview is completely confidential.

If you are matter-of-fact in your approach, you probably will not encounter any problems. People are used to giving such information about themselves to various agencies, so that gathering such data presents much less difficulty than new interviewers often imagine.

7. Don't Knows and Refusals

When a respondent tells you "I don't know" it can mean any number of things. For instance,

a. The respondent does not understand the question and answers "don't know" to avoid saying he or she doesn't understand.
b. The respondent is thinking the question over and says "don't know" to fill the silence and to give him or her time to think.
c. The respondent may be trying to evade the issue because he or she may be uninformed or may give the wrong answer or because the question seems too personal.
d. The respondent really does not know or have an opinion on the subject.

Use an expectant pause, a reassuring remark (e.g. “Well, we’re just interested in your ideas about this.”), repeating the question, or asking a neutral question (e.g. “What are your ideas about this?”) to encourage the respondent to answer whenever possible.

There are times when, despite all efforts, the participant cannot give an answer to a question. In these cases, this non-answer must be noted as well by circling the code for don’t know (“DK”).

Occasionally, a respondent may refuse to answer a question. When this occurs, try the same reassuring remarks or probes that you would use for a “don’t know” situation. If the respondent still refuses to answer, note the refusal by circling the code for refused (“REF”).

The paper questionnaire and all forms should be completed in black ink. Do not erase or block-out mistakes. Simply use one line to cross out the mistake and indicate the correct answer.

There are important rules about the way a statement or question is formatted that tell the interviewer how it should be read to the participant or whether it should be read at all.

5. Interviewer Instructions

Most interviews will be conducted with the assistance of a laptop computer running CATI software. Under these conditions, the software will display the questions to be read, and entry fields for responses. The software will force the appropriate skip patterns depending upon the previous responses, minimizing the margin of error.

In the event a paper form must be used - Instructions to the interviewers are placed throughout the questionnaire to help the interviewer move through the questionnaire or to select appropriate responses. The following interviewer instructions are included in the survey.

Instruction	**Meaning**
Go to Q-Number	Proceed to the next question, which is Q-Number
Skip to Q-Number	Skip the next question(s) and go directly to Q-Number
Enter Number of Times	Record the exact number of times for the category
If ‘Condition’ then Skip To Q-Number	If the condition is true, go directly to Q-Number. Otherwise, proceed to the next question.
Read only if necessary	Read the categories only if respondent needs them to answer properly
Other Instructions	Follow the directions specified

The instructions may be conditional on the response option chosen. Follow the instruction on the same line as the selected response. Other instructions may occur before a question, indicating which respondents should be asked the question and to what question others should skip.

11.4D Conducting the Interview: Off-site Instructions

In the event that the interview is conducted off-site (e.g., at a participants' home), the interviewer will bring a prepared laptop computer and a portable case containing backup paper copies of the surveys. The interviewer will travel with a nurse, and the interview and blood draw and urine collection will be conducted during the same session. Beyond these differences, the interview will be conducted in a synonymous manner as per the guidelines in Sections A and B.

11.5 Complete the Blood Draw

Blood draws will be completed during the same appointment as the interview, whether on-site or off-site. Adopting this practice should increase efficiency and ensure a high participation rate. Blood collection procedures are described in the **Section 12.0.**

11.6. Complete Preliminary Results Form

1. Complete preliminary results form with the height, weight and blood pressure measurements

2. If any of the results are abnormal a member of the nursing staff will explain the problem and arrange for referral as needed.

3. Other results will be mailed to respondents when they are available.

11.7. Distribute Gift Card(s)

1. Give the gift card(s) to respondent.

2. Have Respondent sign for the Gift Card(s).

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11.8. Non-Participant Form/on the phone?

If the biomonitoring participant in the household does not want to participate in the study ask them if they would answer just a few questions as part of the non-participant form. The form includes the following items: gender, race, age. Return the non-participant form and contact sheet to the study office.

11.9. Quality Control

Quality control will be conducted at every opportunity to ensure effective communications with study participants and among personnel, as well as verify the validity of acquired data.

With regards to telephone contact - the contractor's call area is supervised, and all calls are recorded.

With regards to on and off-site interviewing - The RedCap® software employed in this study will have preset response ranges, and will not allow the interviewer to proceed unless a response has been entered. Any questions that require further clarification will be asked again at the end of the interview. Additionally, the CATI will generate a subset of questions at the end of the survey with the specified responses, and the interviewer will ask these questions again as a means of checking for keystroke errors. For this method, the final answer is considered the true answer.

Participants must bring a valid photo ID or the study letter (addressed to him/her) in order to receive compensation. Implementing this will verify that the correct individuals are completing the interview and blood draw.

Attachment 12.

13.0 Data Management and Security

This section of the MOP describes the computer system and data management approach that will be used to support the study and details how data are to be collected, entered (e.g., if eCRFs are used), edited or corrected.

Data management for this study described below includes guidance on:

13.1. Collection, delivery, and management of data

13.1a. Use and protection of personally identifiable information (PII)

The study staff-contractor will receive, manage and store PII in an already established record system (System of Records Notice [SORN] No. 09-19-0001 titled "Records of Persons Exposed to Toxic or Hazardous Substances").

The Multi-site Study will be cross-sectional in design, selected from the list of people with without exposure to PFAS-contaminated drinking water from selected sites. For the Multi-site Study, cooperative agreements were awarded to seven recipients. The cooperative agreement recipients will adhere to the same data management and security and privacy stipulations as described for ATSDR staff and for contractor staff in the following sections.

Examples of the data elements to be collected are:

- Participant Information (Name, SSN, DOB, race, sex, address, email, phone number, etc.)
- Survey Information (consent forms, exposure routes, water consumption/source, medial history, education, occupation, etc.)
- Lab Test Results (PFAS concentration values in blood and urine, lipids, liver function test, kidney function test, thyroid hormones, sex hormones, immune function, anti-body response, etc.)
- Children's schools will complete a form about diagnosed learning disabilities and behavioral problems.
- Medical providers will complete a form about conditions the participants have been diagnosed with.

PII is needed for the informed consent process and for reporting results to each parent of a child participant or adult participant. ATSDR will be the final recipient of the PII and will keep participant PII, including SSN, for future studies, which will include potential re-contacting of participants for the

longitudinal data collections. This will require the linking of participant study identity and results from Study A to Study B, etc.

SSN will be collected at enrollment for linkage to medical records and school records. Once the linkage has occurred, the SSN will be kept with other PII in a separate access-restricted and encrypted secure share site. ATSDR will use SSN for tracking and tracing Multi-site Study participants for enrollment in future longitudinal studies. Overall, ATSDR will retain PII such as name, Social Security Number (SSN), current address, phone number, email address, date of birth, and the date of the participant's blood draw and questionnaire completion.

ATSDR will store the PII in a separate master key dataset along with a study-generated ID in a designated CDC/ATSDR encrypted share drive (i.e. MUST share). This dataset will be separate from the dataset containing consolidated data from the questionnaire/survey data, laboratory data on PFAS, clinical biomarkers, neurobehavioral testing and other data used in the statistical analyses. The study-generated ID will be the variable that can link the two datasets if necessary. PII will not be linked with files used for statistical analysis and will not appear in any reports generated from this data set.

CDC/ATSDR encrypted laptops will be provided to contractor to safely receive the participants' information and survey data. Contractors will be responsible for obtaining access to CDC/REDCap via SAMS, creating a database in CDC/REDCap (approved by CDC/ATSDR OCISO for collecting and storing PII except for SSN), developing data collection forms, and administering the data collection and delivery. Grantees may collect information in several modes: (1) hardcopy and then scanned or entered into databases (informed consent, update contact information, several forms to collect study data during the appointment, neurobehavioral test battery results); and (2) through electronic means (CAPI/CATI programmed into REDCap - eligibility screening scripts, appointment reminder telephone calls, adult and child questionnaires). Contractors will receive data from grantees, enter them into CDC/REDCap database, and transfer the data via VPN/CITGO to the designated encrypted CDC/ATSDR MUST share. At the end of study, once all data sets have been delivered to ATSDR and confirmed study PI, contractor will delete all data sets in CDC REDCap database.

All laboratories involved in biochemical analyses will receive biological specimens with participants' study-generated ID only.

The legal authority to use SSN is covered under the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA) and Superfund Amendments and Reauthorization Act of 1986 (SARA). Legal authorities governing information use and disclosure specific to the system and program are covered under the above laws and also under Consolidated Appropriation Act of 2018 and Public Health Service Act.

Note: Per the informed consent, participants may contact the ATSDR PIs with any concerns or questions about the study. The phone number will be provided. In addition, ATSDR has provided information for the CDC/ATSDR Human Research Protection Helpline at (800) 584-8814, with instructions to specify the reason for the call and to leave name, contact information, and a description of the concern.

The individual may be directed to contact the system manager to identify the record and specify the information being contested, the corrective action sought, and the reasons for requesting the correction, along with supporting information to show how the record is inaccurate, incomplete, untimely, or irrelevant. If an incident has occurred, the system manager will report the potential incident to the CDC Security Incident Response Team and the Privacy Officer. The security manager will serve as the POC to resolve the individual's concerns.

13.1b. Data Delivery/Flow

Grantees will be required to deliver the data to ATSDR in a standard format developed and provided by the contractor. Once receiving the data from grantees, contractor' study staff will follow checks and quality control procedures for data entry into CDC/REDCap. Grantees may be required to send a sample of hardcopy data collection forms to ATSDR for data entry quality check purposes. Only authorized study staff will receive permission to enter or manipulate the study data.

ATSDR will work with the study staff to resolve missing values and other data issues.

The study staff will also keep and deliver a shipping log of blood specimens sent to the NCEH laboratory and the commercial laboratory in Microsoft Excel format. The log will include the include vial type, volume, ID code, date, and carrier details.

ATSDR will receive lab results from the NCEH DLS laboratory via CDC/ATSDR intranet connection. From the commercial laboratory the data will be uploaded through ATSDR approved methods and then stored in the encrypted MUST Share at the CDC/ATSDR. The lab dataset will be merged by study ID with the questionnaire data to create a combined questionnaire and lab dataset.

Figure 1. Data flow diagram

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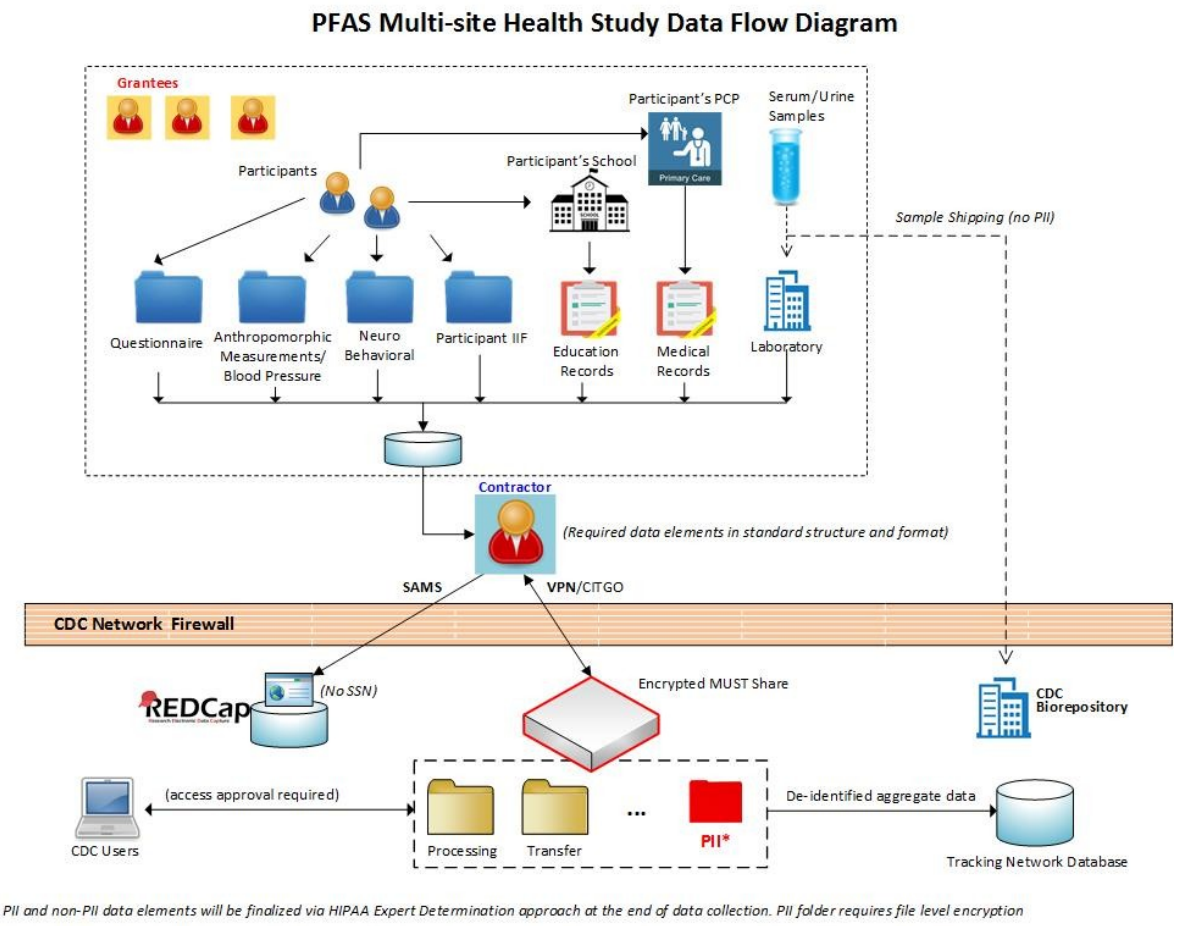

Final datasets will be sent to ATSDR encrypted MUST share, and the contractor will deliver to ATSDR the code (e.g. SAS code for data processing) and the master key dataset by which the response data are potentially relinkable to PII.

Consent forms that collect the signatures of participants will be paper instruments and the adult participant or parent of the child participant will receive a copy of the consent form. Height, weight, and other applicable body measures and blood pressure will be recorded on a paper form and transferred to an electronic form.

13.1. c. Data quality control checks

Data quality control checks may identify potential data anomalies such as:

- Missing data or forms
- Out-of-range or erroneous data

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- Inconsistent and illogical dates over time
- Data inconsistency across forms and visits
- Not completing all fields of a "completed form" or no reason for missing data is provided

Contractor will complete data quality control checks. Only authorized personnel will have access to modify any collected data. Permission from study data steward and study PI will be required; log of all PII access activities (refer to section 13.3 for detailed information that needs to be included in the log) will be required.

13.1c Access Controls and Security

Per the Multi-site Study Rules of Behavior, the study PI, will determine which users will be able to access the data and the specific data they will need based on their role and research goals/priorities. Least privilege access will be employed, and users will only be given access to the minimum data required for their particular analysis. Once approved by study PI, the study data manager will set up or grant appropriate permissions to users.

The contractor Project Director and Project Manager will be responsible for all required staff training and certification, periodic checks of procedures and data collection methods, privacy, and security of data, as well as access of assigned personnel to different types of data. For this information collection, all study staff will be under the direct supervision of the ATSDR on-site supervisor.

The contractor study staff will obtain appropriate office space for the blood draws, clinical assessments, questionnaire, neurobehavioral batteries administration, secure storage of questionnaires, medical and school records, and storage of blood specimens (including refrigeration) prior to shipment to the NCEH and clinical commercial laboratories.

All data and biological specimens collected in the study are the property of ATSDR. *Methods to ensure least privilege access to the study information will be in place; therefore, access to identifiable information will be role-based on a need-to-know basis for the contractor investigators.*

Once collected from the participant, all hardcopy informed consents and data collection forms will be stored in locked files in locked rooms in the study office and at ATSDR. The scanned copies will be uploaded to ATSDR designated MUST share on a daily basis, and the hardcopies will be physically delivered to ATSDR either at the end of data collection or upon request by Principal Investigators. Hard copies must be sent to ATSDR when no longer needed in the field via service that provides for tracking and delivery signature. Usually they will be mailed in batches and not individually.

Upon completion of the project and once the ATSDR has received all approved study related paper documents, the recipient will destroy those hardcopy documents not necessary to complete the study analyses or to contact study participants.

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13.1d. Data Security Measures at ATSDR

Data security measures at ATSDR will comply with the CDC/ATSDR Protection of Information Resources Policy and the CDC/ATSDR IT Security Program Implementation Standards. These policies apply to all authorized ATSDR employees. All incidents involving a suspected or confirmed breach of PII must be reported to OCISO according to the policy titled OCISO/CDC Standard for Responding to Breaches of Personally Identifiable Information (PII).

The CDC/ATSDR issues identity credentials based on the Federal Information Processing Standards (FIPS) Publication 201 for Personal Identity Verification (PIV) authentication of government employees' identities. Security measures for physical access to secured facilities include the use of PIV Cards, security guards, and closed circuit TV monitoring.

CDC/ATSDR policy requires employees to gain authorized logical access to its information systems through a unique electronic identity (User ID). The computer-controlled limits on what can be done by the user are assigned based on program roles and privilege requirements.

Authorized recipient researchers and CDC/ATSDR employees are required to:

- Complete required privacy and information security refresher training.
- Read, acknowledge, sign (if online completion is not available), and comply with the HHS Rules of Behavior, as well as other applicable CDC/ATSDR- and system-specific rules of behavior before gaining access to the CDC/ATSDR's systems and networks.
- Adhere to the requirements set forth in the CDC/ATSDR IT Security Program Implementation Standards, and other security policies and procedures that minimize the risk to CDC systems, networks, and data from malicious software and intrusions.
- Abide by all applicable acceptable use policies and procedures regarding use or abuse of CDC/ATSDR IT resources.

All study records are subject to the ATSDR Comprehensive Record Control Schedule (CRCS), B-371, which contains authorized disposition instructions for ATSDR's administrative and program records. ATSDR is legally required to maintain its program-related records in accordance with disposition instructions contained in this comprehensive records control schedule. These retention periods have a direct impact on completing Freedom of Information Act (FOIA) requests and in applying the requirements of the Privacy Act. The current schedule requires ATSDR to retain and archive program records for a period of 75 years after the end of the study activities.

Records are retained and disposed of in accordance with the CDC Records Control Schedule (B-321) and the ATSDR Comprehensive Records Control Schedule (B-371).

13. 2. Onboarding of Staff

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The contractor will notify the principal investigator as new contract staff join the study. New contractor staff will need to sign the following before beginning work on the study:

- Non-Disclosure Agreement (contractors only and if applicable)
- Study Specific Rules of Behavior

Both documents should be provided to the principal investigator and data manager for secure storage in the Admin folder of the encrypted MUST share.

- OC: Administrative Officer for Center/Division/Branch
- Forms needed: People processing Intake Profile, E-QIP, New User form (http://itsotools.cdc.gov/csb/newuser.aspx)
- Trainings needed: Security Awareness Training (SAT), Safety Survival Skills Training (SSST)
- CITI training required for conducting Human Subjects Research

A Public Trust Level 5 background investigation should at least have been initiated for all staff working with personally identifiable information (PII). Status for all staff should be cleared or complete.

Credential	Status
Background Investigation	Cleared
Network Access	Cleared
SAT Date	Complete
Safety Survival Skills	Cleared

Ensure form1137N for Personal Identification Verification (PIV)/Smartcard has been sent to CDC security (http://isp-v-maso-apps/EForms/download.aspx?ID=2026) in order to get access to CDC networks, computers, and systems. All federal employees working on the study will also need to meet the requirements above.

13.3. Procedures for Requesting Access to Data

The principal investigator (PI) or the data manager of the study shall maintain a data access spreadsheet with the following information at a minimum (spreadsheet/location TBD):

- Date
- First Name
- Last Name
- Contractor/FTE
- CDC User ID
- Approved By
- Approved By Date
- Data Store (share, database, etc.)
- Data Set
- PII included

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- Role (data access level)
- Access Granted By
- Access Granted Date
- Access Removed By
- Access Removed Date

This spreadsheet should be stored in the Admin folder of the encrypted MUST share for this study. When a user requests access to data or changes the type of access to the data, a new entry should be added to this spreadsheet. PI/Data manager must ensure that user have signed the Rules of Behavior for the study before the users are granted access to any study data.

All approvals of access to PII will be reviewed every six months, and the access to PII will be removed immediately when no longer needed.

13.4. Encrypted Multi-User Share Tool (MUST)

Share Location (URI): \\cdc.gov\locker\ATSDR_PFAS_Data\Multisite

13.4.1. User Roles:

- Admin (PI and data manager)
- General User (Contractors & FTE's validating, matching or analyzing data)
- Data Reader (Reviewers and anyone only needing read access)

Additional user roles may be created when needed during the study.

13.4.2. Configuration of Shares.

Following information serves as an example of how sub-shares/folders will be set up on CDC/ATSDR encrypted multi-user share drive to illustrate the data management approaches and activities.

The encrypted MUST share will have the following folders:

- Admin
- Raw Data
- Working Folders
- PII

Folder	Folder Description	Permissions
Admin	Data used only by administrators like spreadsheets, signed RoBs, procedures manuals, etc.	Admin (full), General User (no access), Data Reader (no access)
Raw Data	Data that needs to be preserved in its current form and not altered.	Admin (full), General User (read), Data Reader (read)
Working	Data that is being worked on by staff.	Admin (full), General User (read/write), Data Reader (read)

Role	Description

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Admin	Principal investigators and those that will be administering permissions and encryption for the share
General User	Users that will be working (analyzing, matching, linking, etc.) with the data.
Data Reader	Users that will only need to review the data but will not or should not be able to alter it.

The working folders may have subfolders in it with the CDC user ID of each user working with data. Shares are created and administered through the Multi-User Share Tool (MUST) at http://itsotools.cdc.gov/must/.

The example shares listed below are all encrypted. To confirm a share is encrypted, look at the path name and specifically at the part after "\\cdc\". If the next word is "locker", then the share is encrypted at rest. If the next word is "project", then the share is not encrypted at rest. All shares containing PII should be encrypted.

Multi-User Shares

Path	Description	MUST Group (automatically created by ITSO Tools)	Permissions (automatically assigned by ITSO Tool)	Role(s)
\\cdc.gov\locker\ATSDR_PFAS_Data\Multisite	Share Root	<STUDY NAME>-FC	Full Control (FC) – read, write	Admin
\\cdc.gov\locker\ATSDR_PFAS_Data\ Multisite	Share Root	<STUDY NAME>-RO	Read Only (RO) - read	General User, Data Reader
\\cdc\locker\<STUDY NAME>\admin	Admin Subfolder	<STUDY NAME>.Admin-fc	Full Control (FC) – read, write	Admin
\\cdc\locker\<STUDY NAME>\admin	Admin Subfolder	<STUDY NAME>.Admin-ro	Read Only (RO) - read	None
\\cdc\locker\<STUDY NAME>\working	Working Subfolder	<STUDY NAME>.Working-fc	Full Control (FC) – read, write	Admin, General User
\\cdc\locker\<STUDY NAME>\working	Working Subfolder	<STUDY NAME>.Working-ro	Read Only (RO) - read	Data Reader
\\cdc\locker\<STUDY NAME>\raw_data	Raw_Data Subfolder	<STUDY NAME>.Raw_Data-fc	Full Control (FC) – read, write	Admin
\\cdc\locker\<STUDY NAME>\raw_data	Raw_Data	<STUDY	Read Only	General

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	Subfolder	NAME>.Raw_Data-ro	(RO) - read	User, Data Reader

13.4.3. Granting Access to Shares

The principal investigator or the data manager will grant users access to the MUST encrypted share (depending on the user's role) using the MUST administration tool at http://itsotools.cdc.gov/must/

13.5. Levels of Encryption

13.5.1. File Level Encryption

Any data containing PII must be encrypted at the file level using Symantec Encryption Desktop when not in use. Information about installing the software, configuring the encrypted share, or encrypting individual files can be found in the documents listed below:

- OCISO Installation Procedure for PGP Desktop 10.1.2
- OCISO Quick User Guide for PGP Desktop 10.1.2

Note: When the encrypted share is setup, the PI and the data manager (at a minimum) should be configured as administrators. Anyone who needs to use the share should be configured as a user so that they can decrypt and encrypt files in the share. MUST share permissions will be used to limit what the user can access and modify.

13.5.2. Client Whole Disk Encryption

CDC laptops have whole disk encryption (MS Bitlocker, Check Point, etc.) installed and enabled. CDC desktops do not have this software by default. If a desktop is to be used for processing or storage of study PII, then submit an ITSO helpdesk ticket to inquire whether the desktop is encrypted using whole disk encryption. If it is determined that the desktop is not encrypted, please have ITSO install the software and encrypt the hard drive.

13.6. Requests to Move PII from Encrypted Share

Every effort should be made to keep data in the encrypted MUST share. If data needs to be moved from the share to another location, the move must be approved by the principal investigator (PI) and logged in a PII Transfer spreadsheet. The PI and data manager are responsible for maintaining this spreadsheet. The spreadsheet should contain the following information at a minimum (spreadsheet/location TBD):

- Date
- First Name
- Last Name
- Contractor/FTE
- CDC User ID
- Approved By

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- Approved By Date
- Data Set
- PII?
- Data Transferred To (Laptop Name, System Name, etc.)
- Purpose
- Data Deleted By
- Data Deleted Date
- Notes (Describe how data was deleted)

This spreadsheet should be stored in the Admin folder of the encrypted MUST share for this study.

13.7. Data Sharing and Disclosures

As part of the required "Data Management Plan," ATSDR will create de-identified data sets to share with external researchers. ATSDR plans to execute Data Use Agreement (DUA) with each requester.

Release of de-identified data to outside investigators must be approved by ATSDR. A data use agreement (DUA) will be prepared, detailing the condition of use of the data and proposed analyses for each outside project. The DUA condition of use will specify that ATSDR will not release the link between the study IDs and the participants' PII to the outside researchers.

Disclosures are accounted for according to the referenced SORNs. Disclosures not accounted for in the SORNs will be managed and the procedures established by the system manager. Typically, this will be a manual process where the program keeps track in a spreadsheet.

ATSDR will execute the DUA with outside investigators to specify that:

1. Our data cannot be merged with public data in such a way that individuals may be identified;
2. Our data cannot be enhanced with public data sets with identifiable, or potentially identifiable, data;
3. One of the study investigators listed in Attachment 1 must be a co-investigator on any outside research project to guarantee adherence to the agreed conditions of use; and
4. Each data release will be cleared by a specific IRB request to the investigator's home institution prior to data release.

After the approved project with the outside researchers is completed, further or secondary analyses of electronic datasets can only be undertaken with additional approval(s) from ATSDR. Written confirmation of understanding the conditions of use will be required from the lead scientist and institution. Copies of statistical code and datasets used in statistical analyses by the outside investigators will be kept by ATSDR.

Disclosure of PII to entities outside of CDC (registries, credit bureaus, states, local health departments, etc.) must be approved by the PI and logged in a spreadsheet. The spreadsheet should contain the following information at a minimum:

- Date
- Entity Data Disclosed To

Attachment 12.

- Entity POC Name
- Entity POC Email
- Entity POC Phone Number
- Approved By
- Approved By Date
- Data Set
- PII?
- Disclosure Purpose
- Data Disclosed By
- Data Disclosed Date
- Data Transfer Method
- Approved by ISSO
- ISSO Approval Date
- Notes

Disclosures should not be made without a fully executed data use agreement (DUA). DUA's and the disclosure spreadsheet are maintained by the principal investigator and data manager. This spreadsheet, DUA's, and any related disclosure documentation should be stored in the Admin folder of the encrypted MUST share for this study.

No data should be disclosed with any outside entity until the ISSO has determined that adequate controls exist to protect the data in transit. Written approval (usually via email) should be maintained in the Admin folder of the encrypted MUST share for the study. Approval should also be noted in the disclosure spreadsheet.

13.8. Securely Receiving/Sending Data

Use CDC's Secure Access Management System (SAMS) electronic authentication level 3 to electronically send or receive PII. https://sams.cdc.gov Use of systems or methods, other than SAMS, to electronically send or receive PII must be approved in writing by the NCEH/ATSDR Information Systems Security Officer (ISSO).

13.9. De-identification of Data

At the end of data collection, data manager will lead and coordinate the re-identification risk assessment for the whole data set to evaluate and finalize the PII in the study data set. Once PII is finalized, all PII will be separated from non-PII data and stored and managed on the encrypted MUST share following CDC security policy and requirements.

13.10. Incident Response

Incidents involving the study data or systems storing, processing or transmitting this data should be reported to the CDC Computer Security Incident Response Team within 1 hour. Definitions of an incident can be found in the CDC security awareness training and in the references below.

Computer Security Incident Response Team (CSIRT)

Attachment 12.

Email: csirt@cdc.gov
Phone: 866-655-2245

References

Computer Security Incident Response: Host Isolation, Removal, and Mitigation (CDC-IS-2009-01)
CDC Information Security Enterprise Incident Response Plan Version 5.2

13.11. Privacy

Background

The study is a Privacy Act system covered by System of Records Notice (SORN) 09-19-0001 Records of Persons Exposed or Potentially Exposed to Toxic or Hazardous Substances, HHS/ATSDR (https://www.federalregister.gov/documents/2011/01/25/2010-33004/privacy-act-of-1974-report-of-modified-or-altered-system-of-records)

13.11.1. Review of PII for Accuracy and Relevancy

ATSDR personnel will determine whether the PII collected via consent/parental permission/assent forms and questionnaires are accurate. Participants will be provided ATSDR contact information to allow them to inform ATSDR if their contact information changes (e.g., if they move their residence or update a phone number). These procedures are included in the administrator's guide. If ATSDR conducts a new study, the agency may employ tracking and tracing methods using SSN to obtain updated PII.

13.11.2. Inquiries

Any inquiries from individuals related to their PII in this study will be reviewed by the study PI's. The PI's will decide what action to take (update information, remove the individual's information, etc.) and communicate that decision to the individual within 60 days.

If an individual is concerned that his/her PII has been used inappropriately and communicates that to the CDC, the study PI will evaluate the concern and report the incident to the CDC Chief Privacy Officer within 48 hours.

13.12. Email Usage and Web Browsing

Users that are processing study data that contains PII should not browse the web or check email on their computer/laptop. Instead, then should use citgo.cdc.gov for these activities.

13.13. Out-Processing of Staff

Attachment 12.

13.13.1. Notification

The contractor should notify the contracting officer's representative (COR) and the PI when contract staff are changing roles in the study, leaving the project, or leaving CDC. Official out-processing should occur in People Processing (https://peopleprocessing.cdc.gov/) for users leaving CDC.

13.13.2. User System Access

If a user's role changes or if the user leaves the project or CDC, the PI and data manager will review the data access spreadsheet. Appropriate actions (remove or change access for the user) should be taken by the PI and data manager and the spreadsheet updated.

13.13.3. Return of Equipment

The PI, the data manager, and the COR should ensure that all equipment is returned when a user leaves CDC or the project. Equipment should not be transferred to another center, division, etc. but should be returned to the PI or COR to be securely erased (reimaged).

13.13.4. PII Housekeeping

The PI and the data manager should review the PII Transfer spreadsheet when a user leaves CDC or the project. The PI and data manager should ensure that PII is removed for each entry in the spreadsheet and update the spreadsheet accordingly.

Attachment 12.

14.0 Study Completion and Close-Out Procedures

This section of the MOP outlines the Study Completion and Close-out procedures. This include the following:

- Contractor and the ATSDR will verify that study procedures have been completed, data have been collected, and study intervention(s) and supplies are returned to the responsible party or prepared for destruction.
- Assurance that all data queries have been completed will be provided by the contractor in form of the draft final dataset and report. Reviews and changes/revisions of those documents and acceptance by government will complete these task.
- Assurance will be provided by contractor that correspondence and study files are accessible for external audits.
- Assurance that the study records (those that are not required to be destroyed or deleted, See Section 13) are maintained and any relevant study information reported to the CDC.
- Assurance that the study investigator will notify the IRB of the study's completion and store a copy of the notification.
- Preparation of a report summarizing the study's conduct (see above).
- Participant notification of the study completion.

15.1 Participant Notification

Per study protocol all participants that were able to provide blood sample will receive their individual results for PFAS analyses and clinical biomarkers. They will also be notified via Multi-site CAP of study results published in peer reviewed publication(s) by study staff.

Attachment 12.

15.0 MOP Maintenance

Each page of the MOP is numbered, dated, and contain a version number to facilitate any changes and/or additions. The MOP will serve as a history of the project, documenting the time and nature of any changes in procedures and policies.

See MOP Modification Log Template in Appendix D.

Attachment 12.

BIBLIOGRAPHY

For additional information, please refer to the resources listed below.

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Attachment 12.

RELEVANT WEB SITES

Food and Drug Administration:
http://www.fda.gov/cber/guidelines.htm

http://www.fda.gov/ora/compliance_ref/part11/

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

Gene Therapy, Stem Cells and Fetal Tissue:
http://grants.nih.gov/grants/policy/gene_therapy_20000307.htm

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-050.html

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-026.html

Information Required in NIH Grant Applications:
http://grants.nih.gov/grants/policy/policy.htm

NIH Policies for Monitoring Clinical Research:
http://grants.nih.gov/grants/guide/notice-files/not99-044.html

http://grants.nih.gov/grants/guide/notice-files/not98-084.html

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

http://grants.nih.gov/grants/guide/notice-files/not99-107.html

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-053.html

Implementation of NIA Policies for Human Intervention Studies
http://www.nia.nih.gov/research/dea/implementation-policies-human-intervention-studies

Guidelines for Writing Informed Consent Documents
http://ohsr.od.nih.gov/info/sheet6.html

Attachment 12.

APPENDIX A - ACRONYM GLOSSARY

Adverse Event (AE) – Any untoward or unfavorable medical occurrence in a clinical research study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Case Report Form (CRF) – A printed, optical, or electronic (eCRF) document designed to capture all protocol-required information for a study.

Code of Federal Regulations (CFR) - is an annual codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government.

Coordinating Center (CC) – A group organized to coordinate the planning and operational aspects of a multi-center clinical trial. CCs may also be referred to as Data Coordinating Centers (DCCs) or Data Management Centers (DMCs).

Data and Safety Monitoring Board (DSMB) –A group of individuals independent of the study investigators that is appointed by the NIA to monitor participant safety, data quality and to assess clinical trial progress.

Food and Drug Administration (FDA) – An agency within the U.S. Department of Health and Human Services (DHHS) responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, nation's food supply, cosmetics, and products that emit radiation.

Good Clinical Practice (GCP) – A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule – The first comprehensive Federal protection for the privacy of personal health information. The Privacy Rule regulates the way certain health care groups, organizations, or businesses, called covered entities under the Rule, handle the individually identifiable health information known as protected health information (PHI).

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) – An independent body constituted of medical, scientific, and nonscientific members whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, protocols and amendments, and of the methods and material to be used to obtaining and documenting informed consent of the trial participant.

Manual of Procedures (MOP) – A "cook book" that translates the protocol into a set of operational procedures to guide study conduct. A MOP is developed to facilitate consistency in protocol implementation and data collection across study participants and clinical sites.

Principal Investigator (PI) - The individual with primary responsibility for achieving the technical success of the project, while also complying with the financial and administrative policies and regulations

associated with the award. Although Principal Investigators may have administrative staff to assist them with the management of project funds, the ultimate responsibility for the management of the sponsored research award rests with the Principal Investigator.

Quality Control (QC) – The internal operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of trial related activities have been fulfilled (e.g., data and form checks, monitoring by study staff, routine reports, correction actions, etc.)

Safety *Officer (SO)* - The Safety Officer is an independent individual, usually a clinician, who performs data and safety monitoring activities in low-risk, single site clinical studies. The Safety Officer advises NIA Program Director regarding participant safety, scientific integrity and ethical conduct of a study.

Serious Adverse Event (SAE) – Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Standard Operating Procedure (SOPs) – Detailed written instructions to achieve uniformity of the performance of a specific function across studies and patients at an individual site.

Appendix B - Sample Screen Log

Study: [Study Name]
Site: [Site Name]
Investigator: [Investigator Name]

Screening Number	Date of Birth	Gender	Screening Date	Screening Status (use codes below)	Consent Obtained	Enrolled (if no, indicate reason from codes below)	Date Enrolled
☐☐☐☐	/ / mm/dd/yyyy	☐ M ☐ F	/ / mm/dd/yyyy		☐ Yes ☐ No	☐ Yes ☐ No	/ / mm/dd/yyyy
☐☐☐☐	/ / mm/dd/yyyy	☐ M ☐ F	/ / mm/dd/yyyy		☐ Yes ☐ No	☐ Yes ☐ No	/ / mm/dd/yyyy
☐☐☐☐	/ / mm/dd/yyyy	☐ M ☐ F	/ / mm/dd/yyyy		☐ Yes ☐ No	☐ Yes ☐ No	/ / mm/dd/yyyy
☐☐☐☐	/ / mm/dd/yyyy	☐ M ☐ F	/ / mm/dd/yyyy		☐ Yes ☐ No	☐ Yes ☐ No	/ / mm/dd/yyyy
☐☐☐☐	/ / mm/dd/yyyy	☐ M ☐ F	/ / mm/dd/yyyy		☐ Yes ☐ No	☐ Yes ☐ No	/ / mm/dd/yyyy

Sample Screen Status Codes:

1-Eligible

2-Eligible, declined participation
3-Not Eligible
4-Eligible, lost to follow-up
5-Other, specify in space provided

If not eligible, Reason:

1-Inclusion # (specify)

2-Exclusion# (specify)
3-Other (specify)

Appendix C - Sample Schedule of Events

Visit Description	Screening	*TP	*TP	*TP	*TP	*TP	*TP	*TP	**FU	**FU	**FU	**FU	**FU	**FU
Study Visits/ Study days (or weeks)	Visit-1 Day-14 to Day -1	Visit 1 Day 0	2 W1	3 W2	4 W3	5 W4	6 W8	Final Visit W10	8 W12	9 W14	10 W16	11 W18	12 W20	13 W22
Informed Consent	X													
12-lead EKG	X				X			X	X					X
Medical History	X													
Prior Medications	X													
Physical Exam	X							X						
Vital Signs	X							X						
Chemistries	X		X	X	X			X	X					X
Liver Function Tests	X		X	X	X			X	X					X
Hematology	X		X	X	X			X	X					X
Pregnancy Test	X				X			X	X					X
Investigational Agent Administration		X	X	X	X	X	X	X						
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Study completion														X

*TP – Treatment Phase
**FU – Follow-up Phase

Appendix D - Sample MOP Modification Log

MOP MODIFICATION LOG

Section #	Version #	Date Modified	Page #	Text Location	Brief Modification Summary

Appendix E - Examples of Administrative Forms

An Administrative Form constitutes any form that would not be included in the study database. The following is a list of administrative forms that should be considered for a study. Given that each study is unique, forms could be omitted and/or added at the investigator's discretion depending on the nature of the study.

Participant Identification Code List - Used to document the participant's study identification number, name, and other identifying information. Must be stored securely and separate from research records since it is the link between a study ID and participant's name.

Record of Destruction of Clinical Product* - This log is used to document the destruction of any unused study drug. The date and time of incineration as well as how many vials/pills were incinerated must be recorded. This record should be attached to the Study Drug Accountability Record.

Screening and Enrollment Log - Used to list participants screened; includes those who fail screening and those who are enrolled.

Site-Signature Log /Delegation of Authority Log* **-** Used to list all study personnel and their specific responsibilities, signatures, and dates of obligation during the conduct of a clinical research study. ***Note***: For a template form, please see the NIA Toolbox Study Forms page.

Site Visit Log - Records individuals visiting the site. The most common reasons for visits are site initiation, monitoring, training, and close-out.

Study Drug Accountability Record* – Records help ensure that study drugs have not gone astray and help find them if they do. This record should be maintained in the Pharmacy by the research pharmacist and must not be shared with other members of the study team.

Telephone Contact Log - To record and track study-related telephone contact discussions with a study participant.

Training Log* **-** Documents study-specific training completed by staff exhibiting their qualifications to perform tasks involved in the clinical research study. Other training may also be listed on this log.

*Forms could also be considered a regulatory document rather than an administrative form.

Appendix F – CDC IRB Consent Form

Attachment 7b1 – Privacy Act Statement

PRIVACY ACT STATEMENT
FOR THE
HUMAN HEALTH EFFECTS OF DRINKING WATER EXPOSURES TO PER- AND POLYFLUOROALKYL SUBSTANCES (PFAS): A MULTI-SITE CROSS-SECTIONAL STUDY (THE MULTI-SITE STUDY)

This statement provides the notice required by the Privacy Act of 1974 (5 USC § 552a(e)(3)).

- **Authority:** The Agency for Toxic Substances and Disease Registry (ATSDR) has the authority to collect this information under the Section 316(a) of the National Defense Authorization Act of 2018 (Public Law 115-91), as amended by Section 315(a) of the John S. McCain National Defense Authorization Act for Fiscal Year 2019 (Pub. L. 115-232).

- **Purpose:** ATSDR is funding this research to study whether exposure to per- and polyfluoroalkyl substances (PFAS) from drinking water might be a public health concern. [Insert study investigators' institution name] is collecting this information on you or your child for:
  - Adult consent, parental permission, and child assent to participate in surveys, tests, and blood and urine collections.
  - Consent for ATSDR and [institution name] to look at your child's school records. This will help to compare study results to school records.
  - Consent for ATSDR and [institution name] to look at your or your child's medical records. We will compare doctors' notes to survey results. This will improve the quality of the study results.
  - Sending your or your child's results back to you.
  - Contacting you for future studies.

Multi-site Study
Privacy Act Statement at Consent
Flesch-Kincaid Readability Score – 8.5
(deleting authority; NCEH spelled out; SORN)

- **Routine Uses:**
  - ATSDR will share these records with the National Center for Environmental Health. NCEH may provide research or support staff, laboratory and statistical analysis, etc.
  - ATSDR and [institution name] may disclose these records to its contractors to locate individuals exposed or potentially exposed to PFAS, and to conduct interviews and other research activities. The contractor must also comply with the requirements of the Privacy Act to protect your or your child's records.
  - Other routine uses as described in System of Records Notice (SORN) No. 09-19-0001 - ''Records of Persons Exposed or Potentially Exposed to Toxic or Hazardous Substances." See https://www.gpo.gov/fdsys/pkg/FR-2011-01-25/pdf/2010-33004.pdf.

- **Disclosure:** Providing this information is voluntary. ATSDR and [institution name] need this information for you or your child to take part in the study. Both institutions need up-to-date contact information to send your or your child's study results. If you permit, ATSDR would like to keep your contact information for future studies.

Participant Initials: _____

Multi-site Study – Parental Permission/Child Assent
Flesch-Kincaid Readability Score –
KEY THINGS – 8.4
Overall – 7.9
Children – 4.5

Attachment 7b2.

Parental Permission and Child Assent Form

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled:*

"Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): A multi-site cross-sectional study "

[INSTITUTION NAME] PRINCIPAL INVESTIGATOR(S): [investigator name(s)]

ATSDR PRINCIPAL INVESTIGATORS: Dr. Marian Pavuk, Dr. Frank Bove

SPONSOR: Agency for Toxic Substances and Disease Registry (ATSDR)

CDC Protocol #7207

KEY THINGS TO KNOW ABOUT THIS RESEARCH

AUTHORITY: Public Law 115-91, the "National Defense Authorization Act of 2018."

PURPOSE: To see if PFAS exposure from drinking water is related to children's health outcomes.

WHO CAN TAKE PART: About 2,000 eligible children, 4-17 years of age, and their parents or guardians.

- ATSDR and [institution name] are enrolling [300] children, 4-17 years of age, who were exposed to PFAS-contaminated water from the [insert site].
- ATSDR and its research partners plan to recruit at least 2,000 children for the Multi-site Study. Those children have had to reside in areas served by PFAS contaminated drinking water or were exposed *in utero* or during breastfeeding when the mother consumed the contaminated drinking water. Drinking water exposure must have occurred within 15 years of the start of the study. The birth mothers for children cannot have or had contact with PFAS chemicals at work.
- Eligible girls who are pregnant may enroll.
- People who are prisoners or under house arrest are not eligible to take part in this study.

Ideally, the parent should be the mother, who can best answer some survey questions about the child's exposures and about the mother's pregnancy and breastfeeding history. A parent can enroll with more than one child. In this case, ATSDR and [institution name] will enroll each child separately along with his or her parent. Parents, if eligible, may also enroll in the adult study.

ATSDR and [institution name] ask children and parents to come to our central study office. We will offer to meet some families at home, if they find travel difficult. They must live within a one-hour drive from the office.

EXPECTED TIME IN THE STUDY: About 2 hours. To save time, your child can do some parts of the study while you do the parent's parts.

PROCEDURES: Trained study staff will take your child's body measures and list your child's medications. You, as the parent, will answer survey questions and behavioral assessments about your child. At the same time, the child will complete his or her own assessments.

ATSDR and [institution name] will collect your child's blood and urine biospecimens. ATSDR will try to analyze blood for PFAS and health tests right away. Urines will be stored until such time that lab methods are developed and scientific evidence shows which PFAS tests will yield useful results. After all tests are done, ATSDR would like to save your child's leftover blood and urine for future studies, and only if you permit.

Participant Initials: _____

If you permit, ATSDR and [institution name] will ask the doctor to verify some of your child's medical history. ATSDR will also look at your child's school records to compare to the assessment results. If your child took part in any PFAS Blood Testing Program, ATSDR would like to get those results.

RISKS: The risks of taking part in this research are minimal. These risks are about the same as those your child would face in daily life. . The risk of giving blood would be the same as in a doctor's office. It may hurt a little when the blood is drawn. Your child may get a bruise where the blood is drawn. We will do our best to prevent these problems.

BENEFITS: There are no direct benefits for your child to be in the study. We will give you the results of his or her blood PFAS and health tests that you may find helpful to share with your child's doctor. We also think that the study will help the [insert site] community better understand the connection between PFAS and health.

CONFIDENTIALITY: ATSDR and [institution name] has taken steps to protect your child's privacy. A Certificate of Confidentiality covers this research. *ATSDR,* [institution name]*, and its contractors cannot be forced to release information that could identify you or your child even under a court order or subpoena (unless you consent to a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.*

IT IS YOUR DECISION: You and your child may freely choose to, or refuse to, take part in this research. During your appointment, you can stop at any time. You and your child can refuse to answer any questions or have your child's blood drawn or urine collected. There is no penalty for refusing to take part or for leaving the study at any time.

FOR QUESTIONS ABOUT THIS STUDY: If you have any questions about the study, or if you and your child decide later that you do not want to take part, please contact [study investigators]at (xxx) xxx-xxxx. They can provide a phone number for a consultation with a health care provider at no cost to you if you would like to discuss your child's results.

FOR QUESTIONS ABOUT YOUR CHILD'S RIGHTS IN RESEARCH OR ABOUT A RESEARCH-RELATED INJURY: For questions about your rights in taking part in this study, call the CDC/ATSDR Human Research Protection Helpline at (800) 584-8814. Be sure to say your call is about CDC Protocol No. 7207. Leave your name, contact information, and a description of your concern.

DETAILS ABOUT THIS RESEARCH

STUDY OVERVIEW/PURPOSE: ATSDR and [institution name] are inviting your child to take part in a research study to find out about the potential health effects of PFAS in the drinking water in your area.

GETTING READY FOR YOUR APPOINTMENT: When study staff screened and told you that your child was eligible, we scheduled your appointment and mailed you a packet with instructions on how to prepare for the appointment.

- On the morning of the appointment, we request that you help your child collect a clean first morning voided urine sample. Bring it to the appointment.
- We also request that your child not eat for at least 8 hours before his or her appointment so that we can collect a fasting blood sample.

- If your child is taking any medications or dietary supplements, we request that you bring them to the appointment. We also as that you note the dates of your child's vaccinations for us to write down.
- If your child participated in a PFAS biomonitoring program in the past, we ask that you bring a copy of the results to the appointment.

WHAT TO EXPECT AT YOUR APPOINTMENT: The whole appointment will take about two hours.

- We will measure your child's height, weight, waist, hip, and blood pressure.
- We will take in your child's urine sample, which you will help your child collect that morning.
- We will collect a fasting blood sample from your child. A trained phlebotomist will draw a small amount of blood from a vein in your child's arm (about 5 teaspoons). We will label your child's samples with a study ID only.

  Certain medical conditions might interfere with our drawing blood or might affect the results of our lab tests. If your child has of one of these conditions, he or she may not be able to take part in all parts of the study. However, he or she can still do the interviews and have a weight, height, waist, hip, and blood pressure measured.

- The questionnaire about your child's exposure and medical history should take about 30 minutes to complete. Parents who also enroll as adults will take a shorter 15-minute questionnaire.
- We will also ask you to complete an assessment of your child's attention and behaviors. It should take about 15 minutes.
- Trained professionals will give your child the behavioral assessments. Although some age groups will only need 30 to 60 minutes, the testing will take about 90 minutes for most children. The tests will be given at a relaxed pace and should not be tiring for your child.

We very much appreciate you and your child taking part in this study. If you complete all parts of the study, we will give you $75 in gift cards as our way of saying thank you. If you and your child complete parts of the appointment, we will provide the following gift cards:

- $25 for body and blood pressure measures, and for blood and urine collection;
- $25 for completed questionnaire; and
- $25 for child/parent completion of the neurobehavioral test battery

QUESTIONS WE WILL ASK: We will ask you questions about your child's health, medications, vaccinations, drinking water habits, and daycare attendance. If you report that your child had certain health conditions, we would like to review your child's medical records to confirm his or her health conditions. We will also ask you about his or her mother's health, pregnancies, and work history. We would like to know more about her pregnancy and breastfeeding of your child.

Participant Initials: _____

We will ask you to complete a parent's assessment of your child's attention and behaviors. We will ask your child to take assessment tests about his or her attention, memory, and behaviors. We will assess IQ for children older than 5 years of age. Education professionals have used these types of assessment tests for many years with thousands of children who often find them fun and enjoyable. We would like to compare your child's school records to the assessment results.

PFAS MEASURED IN BLOOD: We will send your child's blood sample for lab analysis. The lab will measure the levels of specific PFAS in your child's blood.

OTHER BLOOD TESTS: We will send your child's blood to the lab for health tests such as cholesterol, other lipids, liver enzymes, and thyroid hormones. We will also look at allergy markers and vaccine response. Doctors often use these types of tests. They will help us learn more about how PFAS might affect health. For this study, we will not conduct genetic, HIV, or drug testing.

PFAS MEASURED IN URINE: Scientists are learning more about PFAS every day. Your child's urine specimen will be stored until lab methods are developed and the scientific evidence shows which PFAS tests will yield useful results. It might be a year or more before ATSDR decides if and which PFAS tests in urine should be done as part of this research study.

YOUR CHILD'S TEST RESULTS: We will send you a letter with your child's blood PFAS and health test results. We think we will finish all of the lab tests in less than six months after we draw your child's blood. If your child's test results suggest a health problem, we will let you know before we mail the blood test results. Despite the anticipated time delay, ATSDR and [institution name] plans to send a report of your child's urine PFAS.

COSTS: You do not have to pay to let your child be part of this study. The blood tests are free.

MORE ABOUT CONFIDENTIALITY: ATSDR and [institution name] has taken steps to protect your privacy. A Certificate of Confidentiality covers this research. ATSDR is required to protect the privacy of persons who are subjects of this research under subsection 301(d) of the Public Health Service Act (PHSA) [42 USC §241(d)]. *ATSDR and its research partners cannot be forced to release information that could identify you or your child even under a court order or subpoena (unless you consent to a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.*

You should also know that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow ATSDR or [institution name] to release it.

ATSDR and its research partners are required to ensure that any investigator or institution not funded by ATSDR who receives a copy of identifiable, sensitive information protected by a Certificate, understand they are also subject to the requirements of subsection 301(d) of the PHSA.

We will store your answers and test results using a study number, not your child's name. We will keep his or her records in locked files at the study office in [insert site]. ATSDR and its research partners will

protect any computer files with your child's information. Only study staff with a need-to-know will have access to his or her information and test results. All study staff will take training on how to protect the privacy of people who take part in this research.

USE OF COLLECTED INFORMATION: We will write reports or scientific articles about the study results. We will combine everyone's responses to get a picture of the health issues of people across the sites as they may relate to PFAS. These reports or articles will be available to the public after the study is finished. The report results will not identify who took part in the study.

STORING RESIDUAL BIOSPECIMENS AND MULTI-SITE STUDY DATA FOR FUTURE USE:

ATSDR will keep your and your child's contact information and study ID number(s) in a restricted-access secure master dataset. All biospecimens and study data will be coded and stored only with study IDs for data analysis. If you change your mind later and decide not to let us use your biospecimens or data for other projects, you can contact us and we will remove you from the list.

We are ***seeking permission now and will not recontact*** you for the following activities:

- **Additional analyses of stored biospecimens related to this PFAS research:** After we test your child's blood and urine, there may be some left over. Because new scientific knowledge, tests, or methods may arise, we would like to save this leftover blood and urine for additional analyses on exposures or health conditions related to PFAS. We do not plan to report the results of all of these additional or future research tests to you, but we will contact you if the results are clinically important to your child's health.

- **Future analyses by outside investigators:** In addition, ATSDR/[institution name] may release your child's **de-identified research datasets or de-identified blood and urine** samples for future studies related to PFAS to outside investigators under a data use agreement that will prohibit any attempt to identify you or your child as a research subject. In this case, your individual test results will not be reported to you.

We would like ***to keep your contact information for future studies*****.** We would like **to recontact you** to get additional consent for the following types of activities:

- **Studies that require collection of additional data or biospecimens.** After we complete this study we may conduct new research studies. At that time, we may ask your consent to include your child, and your child's data or leftover biospecimens from this current study. We'd like to contact you at that time.**For studies using existing or additional biospecimens for genetic test or whole genome sequencing.** Currently, we have no plans for such tests. However, if such studies are proposed in the future, we would recontact you to request consent for such tests.

Your stored biospecimens will not be used for any commercial activities for profit. All future analyses and studies must adhere to IRB review requirements.

If you do not understand what we are asking you to do, feel free to ask questions now. If you have no further questions and agree to be in this study, please sign the permission and assent form below.

Participant Initials: _____

Child Assent Information about the Multi-site Study

THINGS TO KNOW ABOUT THIS STUDY

WHO IS DOING THIS STUDY: ATSDR is a public health agency that does research at places like [insert site]. [Insert site] has a chemical that got into some of the drinking water. In [insert site], the chemical is called "PFAS."

PURPOSE: In this study, ATSDR and [institution name] will ask you to tell us about your health, to take some assessment tests, and to get your blood tested for PFAS. This way, when ATSDR and [institution name] investigators look at all the results together, we can see if any answers about children's health might relate with their PFAS results.

WHO CAN TAKE PART: ATSDR and [institution name] wants to enroll about 300eligible children, 4-17 years of age, and their parents. We think it is best if your mother comes with you. That is because we will ask a lot of questions about when you were a baby.

EXPECTED TIME IN THE STUDY: About 2 hours. To save time, you can do some parts of the study at the same time as your parent. Before you come to the study, we ask that you not eat for 8 hours. We also ask that you pee in a lab cup at home and bring the sample with you.

WHAT WILL YOU DO: It will be a lot like going to the doctor's. We will measure how tall you are and how much you weigh. We will take your blood pressure and write down your medicines, if you take any. We will take your pee and draw a small blood sample. The blood draw might hurt a little, but for most children, it is not too bad.

Your parent will answer questions about you. At the same time, you will do the assessment tests. They are a lot like puzzles and thinking games that you might find fun to do.

IT IS YOUR DECISION: You are free to decide if you want to do the study. If you start, you can stop at any time. You can refuse to answer any questions. You can decide not to give a blood or urine sample. Nothing bad will happen to you or your parent if you don't join the study.

FUTURE STUDIES: ATSDR and [institution name] may plan to do more studies in the future. Sometimes, ATSDR and [institution name] might want to let you know about a new study or to get your permission to include you, your study data, or your leftover blood and urine, for a new study. To do this, we'd like to contact you then.

Participant Initials: _____

PARENTAL PERMISSION AND CHILD ASSENT (SIGNATURE PAGE 1 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled: "Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): A multi-site cross-sectional study "*
CDC Protocol #7207

FOR OFFICE USE ONLY
Adult Study ID No. |_____| (alias)
Parent Study ID No. |_____|
Child Study ID No. |_____|

I have read and/or have been told about the purpose of the study. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I choose to take part in the study.

By signing below, I agree to the parts of the Multi-site Study that I have checked below:

- [__] Answer study questions about my child.
- [__] Complete a parent assessment of my child's attention and behaviors.
- [__] Have my child take a test for attention and behaviors.
- [__] Have my child, who is > 5 years of age, take an IQ test; **or** [__] My child is ≤ 5 years of age.
- [__] Allow ATSDR and [institution name] to review my child's school records.
- [__] Allow ATSDR and [institution name] to review my child's medical records.
- [__] Give ATSDR and [institution name] a copy of any PFAS Blood Testing Program results; if available; [__] My child has not participated in a PFAS Blood Testing Program.
- [__] Have my child provide a blood sample and have it tested.
- [__] Have my child provide a urine sample and have it stored.

_____ Parent or Guardian's Name (Print)	_____ Child's Name (Print) (≥ 7 years old)
_____ Parent or Guardian's Signature Date	_____ Child's Signature Date
	|__|__|__| - |__|__| - |__|__|__|__| Child's Social Security Number
	|__|__| - |__|__| - |__|__|__|__| MM DD YYYY Child's Date of Birth

PARENTAL PERMISSION AND CHILD ASSENT (SIGNATURE PAGE 2 OF 2)

Participant Initials: _____

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled: "Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): A multi-site cross-sectional study "*

CDC Protocol #7207

FOR OFFICE USE ONLY
Adult Study ID No. |_____| (alias)
Parent Study ID No. |_____|
Child Study ID No. |_____|

I have read and/or have been told about ATSDR's plans for using my child's study data and leftover biospecimens in the future. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I understand that ATSDR will follow CDC IRB requirements for these new studies.

By signing below, I agree to the additional uses of my child's Multi-site Study data and leftover biospecimens that I have checked below:

[__] ATSDR and [institution name] can contact me about new studies.

[__] ATSDR and [institution name] can use my child's study data and his or her leftover blood and urine for new studies about PFAS.

[__] ATSDR and [institution name] can use my child's study data and his or her leftover blood and urine for new studies that are not about PFAS.

_____ Parent or Guardian's Name (Print)	_____ Child's Name (Print) (≥ 7 years old)
_____ Parent or Guardian's Signature Date	_____ Child's Signature Date

Participant Initials: _____

Multi-site Study
Parental Consent Release Student Info
Flesch-Kincaid Readability Score – 8.1

Attachment 7b3.

Multi-site Study

PARENTAL CONSENT TO RELEASE STUDENT INFORMATION

Under the Family Educational Rights and Privacy Act (FERPA), the Agency for Toxic Substances and Disease Registry (ATSDR) and [institution name] are seeking parental consent for the release of your child's school records. ATSDR and [institution name] will compare your child's school records to some of his or her research test results from the Multi-site Study.

The only type of information that is to be released under this consent is:
_____ Individualized Education Program (IEP)
_____ IEP Evaluation Report ("Full Individual Evaluation" or "FIE")
_____ Independent Educational Evaluation (IEE)

ATSDR and [institution name] plan to send trained study staff to the school indicated on this form. The staff will perform school record abstractions limited to the above information. You have a right to inspect any written records released pursuant to this consent. You may revoke this consent upon providing written notice to the Education Official and School that you permitted to release you child's school records. Until it is revoked, this consent shall remain in effect. Until such time, your child's school records will be provided to ATSDR and [institution name] until the study is over.

By signing below, you permit:

Name of Official: _____School: _____
to release your child's school records to the study investigators [insert name(s)]. You may contact them with any questions at [study telephone number].

Name of Student (print): _____ Student ID No. _____

Address of Student: _____

City: _____ State: _____ Zip Code: _____

Name of Parent or Guardian (print): _____

Signature of Parent or Guardian: _____

Date of Consent: |__|__|/|__|__|/|__|__|

Participant Initials: _____

Multi-site Study – Adult Consent
Flesch-Kincaid Readability Score –
KEY THINGS – 8.2
Overall – 8.3

Attachment 7b4.

Adult Consent Form

TITLE OF RESEARCH: *""**The Multi-site Study**" formally titled: "Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): A multi-site cross-sectional study "*

[INSTITUTION NAME] PRINCIPAL INVESTIGATOR(S): [investigator name(s)]

ATSDR PRINCIPAL INVESTIGATORS: Dr. Marian Pavuk, Dr. Frank Bove

SPONSOR: Agency for Toxic Substances and Disease Registry (ATSDR)

CDC Protocol #7207

KEY THINGS TO KNOW ABOUT THIS RESEARCH

AUTHORITY: Public Law 115-91, the "National Defense Authorization Act of 2018."

PURPOSE: To see if PFAS exposure from drinking water is related to adult health outcomes.

WHO CAN TAKE PART: Eligible adults, ≥ 18 years of age. ATSDR and [institution name] ask you to come to our central study office.

- ATSDR and [institution name] are enrolling 1,000 adults, ≥ 18 years of age who were exposed to PFAS-contaminated water from the [insert site].
- ATSDR and its research partners plan to recruit at least 6,000 adults for the Multi-site Study. Those persons had to reside in areas served by PFAS contaminated drinking water or were exposed in utero or during breastfeeding when the mother consumed the contaminated drinking water.
- Drinking water exposure must have occurred within 15 years of the start of the study. Persons who were ever employed as a firefighter, ever participated in fire training exercises using AFFF foam, or were ever employed at industrial facilities that used PFAS chemicals in the manufacturing process will be excluded.
- Eligible females who are pregnant may enroll.
- People who are prisoners or under house arrest are not eligible to take part in this study.
- An eligible adult can also enroll as a parent of one or more eligible children.

We will ask you to come to our central study office. We will offer to meet some adults at home, if they find travel difficult. They must live within a one-hour drive from the office.

EXPECTED TIME IN THE STUDY: About 45 minutes.

PROCEDURES: Trained study staff will take your body measures and list your medications. You will answer survey questions.

ATSDR and [institution name] will collect your blood and urine biospecimens. ATSDR and [institution name] will try to analyze blood for PFAS and health tests right away. Urines will be stored until such time that lab methods are developed and scientific evidence shows which PFAS tests will yield useful results. After all tests are done, ATSDR and [institution name] would like to save your leftover blood and urine for future studies, and only if you permit.

If you permit, study staff will ask the doctor to verify some of your medical history. If you took part in any PFAS Blood Testing Program, ATSDR would like to get those results.

RISKS: The risks of taking part in this research are minimal. These risks are about the same as those you would face in daily life. The risk of giving blood would be the same as in a doctor's office. It may hurt a little when the blood is drawn. You may get a bruise where the blood is drawn. We will do our best to prevent these problems.

Participant Initials: _____

BENEFITS: There are no direct benefits for you to be in the study. We will give you the results of your blood PFAS and health tests that you may find helpful to share with your doctor. We also think that the study will help the [insert site] community better understand the connection between PFAS and health.

CONFIDENTIALITY: ATSDR has taken steps to protect your privacy. A Certificate of Confidentiality covers this research. *ATSDR and its research partners cannot be forced to release information that could identify you even under a court order or subpoena (unless you choose to a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.*

IT IS YOUR DECISION: You may freely choose to, or refuse to, take part in this research. During your appointment, you can stop at any time. You can refuse to answer any questions or have your blood drawn. There is no penalty for refusing to take part or for leaving the study at any time.

FUTURE STUDIES: ATSDR and [institution name] may plan to do more studies in the future. Sometimes, ATSDR and [institution name] might want to let you know about a new study or to get your permission to include you, your study data, or your leftover blood and urine, for a new study. To do this, we'd like to contact you then.

FOR QUESTIONS ABOUT THIS STUDY: If you have any questions about the study, or if you decide later that you do not want to take part, please contact [study investigators] at (xxx) xxx-xxxx. They can provide a phone number for a consultation with a health care provider at no cost to you if you would like to discuss your results.

FOR QUESTIONS ABOUT YOUR RIGHTS IN RESEARCH OR ABOUT A RESEARCH-RELATED INJURY: For questions about your rights in taking part in this study, call the CDC/ATSDR Human Research Protection Helpline at (800) 584-8814. Be sure to say your call is about CDC Protocol No. 7207. Leave your name, contact information, and a description of your concern.

DETAILS ABOUT THIS RESEARCH

STUDY OVERVIEW/PURPOSE: ATSDR and [institution name] are inviting you to take part in a research study to find out about the potential health effects of PFAS in the drinking water in your area.

GETTING READY FOR YOUR APPOINTMENT: When study staff screened and told you that you were eligible, we scheduled your appointment and mailed you a packet with instructions on how to prepare for the appointment.

- On the morning of the appointment, we request that you collect a clean first morning voided urine sample. Bring it to the appointment.
- We also request that you not eat for at least 8hours before your appointment so that we can collect a fasting blood sample.
- If you are taking any medications or dietary supplements, we request that you bring them to the appointment.
- If you participated in a PFAS biomonitoring program in the past, we ask that you bring a copy of the results to the appointment.

WHAT TO EXPECT AT YOUR APPOINTMENT: The whole appointment will take about 45 minutes.

- We will measure your height, weight, waist, hip, and blood pressure.

- We will take in your urine sample, which you will collect that morning.

- We will collect a fasting blood sample. A trained phlebotomist will draw a small amount of blood from a vein in your arm (about 7 teaspoons). We will label your samples with a study ID only.

  Certain medical conditions might interfere with our drawing blood or might affect the results of our lab tests. If you have of one of these conditions, you may not be able to take part in all parts of the study. However, you can still do the interviews and have a weight, height, waist, hip, and blood pressure measured.

- The questionnaire about your exposure and medical history should take about 30 minutes to complete.

We very much appreciate you taking part in this study. If you complete all parts of the study, we will give you $50 in gift cards as our way of saying thank you. If you complete parts of the appointment, we will provide the following gift cards:

- $25 for body and blood pressure measures, and for blood and urine collection; and

- $25 for completed questionnaire.

QUESTIONS WE WILL ASK: We will ask you questions about your health, medications, drinking water habits, and work history. If you report that you had certain health conditions, we would like to review your medical records to confirm these health conditions. For women, we will also ask your reproductive and breastfeeding history.

PFAS MEASURED IN BLOOD: We will send your blood sample for lab analysis. The lab will measure the levels of specific PFAS in your blood.

OTHER BLOOD TESTS: We will send your blood to the lab for health tests such as cholesterol, other lipids, liver enzymes, and thyroid hormones. We will also look at allergy markers. Doctors often use these types of tests. They will help us learn more about how PFAS might affect health. For this study, we will not conduct genetic, HIV, or drug testing.

PFAS MEASURED IN URINE: Scientists are learning more about PFAS every day. Your urine specimen will be stored until lab methods are developed and the scientific evidence shows which PFAS tests will yield useful results. It might be a year or more before ATSDR decides if and which PFAS tests in urine should be done as part of this research study.

YOUR TEST RESULTS: We will send you a letter with your blood PFAS and health test results. We think we will finish all of the lab tests in less than six months after we draw your blood. If your test results suggest a health problem, we will let you know before we mail the blood test results. Despite the anticipated time delay, ATSDR plans to send a report of your urine PFAS.

COSTS: You do not have to pay to be part of this study. The blood tests are free.

MORE ABOUT CONFIDENTIALITY: ATSDR and [institution name] have taken steps to protect your privacy. A Certificate of Confidentiality covers this research. ATSDR is required to protect the privacy of persons who are subjects of this research under subsection 301(d) of the Public Health Service Act

(PHSA) [42 USC §241(d)]. *ATSDR and its research partners cannot be forced to release information that could identify you or your child even under a court order or subpoena (unless you choose to such a release). You should know, however, that ATSDR may tell local authorities if harm to you, harm to others, or if child abuse or neglect becomes a concern.*

You should know that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow ATSDR to release it.

ATSDR, [institution name], and its contractors are required to ensure that any investigator or institution not funded by ATSDR who receives a copy of identifiable, sensitive information protected by a Certificate, understand they are also subject to the requirements of Subsection 301(d) of the PHSA.

We will store your answers and test results using a study number, not your name. We will keep your records in locked files at the study office in [insert site]. ATSDR and its research partners will protect any computer files with your information. Only study staff with a need-to-know will have access to your information and test results. All study staff will take training on how to protect the privacy of people who take part in this research.

USE OF COLLECTED INFORMATION: We will write reports or scientific articles about the study results. We will combine everyone's responses to get a picture of the health issues of people in [insert site] as they may relate to PFAS. These reports or articles will be available to the public after the study is finished. The report results will not identify who took part in the study.

STORING RESIDUAL BIOSPECIMENS AND MULTI-SITE STUDY DATA FOR FUTURE USE:

ATSDR will keep your contact information and study ID number(s) in a restricted-access secure master dataset. All biospecimens and study data will be coded and stored only with study IDs for data analysis. If you change your mind later and decide not to let us use your biospecimens or data for other projects, you can contact us and we will remove you from the list.

We are ***seeking permission now and will not recontact*** you for the following activities:

- **Additional analyses of stored biospecimens related to this PFAS research:** After we test your blood and urine, there may be some left over. Because new scientific knowledge, tests, or methods may arise, we would like to save this leftover blood and urine for additional analyses on exposures or health conditions related to PFAS. We do not plan to report the results of all of these additional or future research tests to you, but we will contact you if the results are clinically important to your health.

- **Future analyses by outside investigators:** In addition, ATSDR/[institution name] may release your **de-identified research datasets or de-identified blood and urine** samples for future studies related to PFAS to outside investigators under a data use agreement that will prohibit any attempt to identify you as a research subject. In this case, your individual test results will not be reported to you.

We would like ***to keep your contact information for future studies*.** We would like to recontact you to get additional consent for the following types of activities:

- **Studies that require collection of additional data or biospecimens.** After we complete this study we may conduct new research studies. At that time, we may ask your consent to include you, and your data or leftover biospecimens from this current study. We'd like to contact you at that time.

Participant Initials: _____

- **For studies using existing or additional biospecimens for genetic test or whole genome sequencing.** Currently, we have no plans for such tests. However, if such studies are proposed in the future, we would recontact you to request consent for such tests.

Your stored biospecimens will not be used for any commercial activities for profit. All future analyses and studies must adhere to IRB review requirements.

If you do not understand what we are asking you to do, feel free to ask questions now. If you have no further questions and agree to be in this study, please sign the permission and assent form below.

ADULT INFORMED CONSENT (SIGNATURE PAGE 1 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled:*
"Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): a multi-site cross-sectional study."

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____|
(alias)
Child Study ID No. |_____|

I have read and/or have been told about the purpose of the study. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I choose to take part in the study.

By signing below, I agree to the parts of the Multi-site Study that I have checked below:

[__] Answer study questions.

[__] Allow ATSDR and[institution name] to review my medical records.

[__] Give ATSDR and[institution name] a copy of my PFAS Blood Testing Program results if available; **or** give ATSDR and [institution name] permission to get my results (if available); [__] I have not participated in a PFAS Blood Testing Program.

[__] Provide a blood sample and have it tested.

[__] Provide a urine sample and have it stored.

_____
Adult's Name (Print)

_____
Adult's Signature Date

|__|__|__| - |__|__| - |__|__|__|__|
Adult's Social Security Number

|__|__| - |__|__| - |__|__|__|__|
MM DD YYYY
Adult's Date of Birth

ADULT INFORMED CONSENT (SIGNATURE PAGE 2 OF 2)

TITLE OF RESEARCH: *"**The Multi-site Study**" formally titled:*
"Human health effects of drinking water exposures to per- and polyfluoroalkyl substances (PFAS): a multi-site cross-sectional study."

CDC Protocol #7207

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____|
(alias)
Child Study ID No. |_____|

I have read and/or have been told about ATSDR's plans for using my study data and leftover biospecimens in the future. I have been given a chance to ask questions and my questions have been answered. I have been given a copy of this form. I understand that ATSDR and [institution name] will follow CDC IRB requirements for these new studies.

By signing below, I agree to the additional uses of my Multi-site Study data and leftover biospecimens that I have checked below:

[__] ATSDR and [institution name] can contact me about new studies.

[__] ATSDR and [institution name] can use my study data and his or her leftover blood and urine for new studies about PFAS.

[__] ATSDR and [institution name] can use my study data and his or her leftover blood and urine for new studies that are not about PFAS.

_____

Adult's Name (Print)

_____

Adult's Signature Date

Multi-site Study
Permission for Medical Record Abstraction
Flesch-Kincaid Readability Score – 11.7

Attachment 7b5.

Parent/Child/Adult Permission for Medical Record Abstraction
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR)
MULTI-SITE STUDY

FOR OFFICE USE ONLY
Adult Study ID No. |_____|
Parent Study ID No. |_____|
Child Study ID No. |_____|

I authorize this health care provider or organization to release protected health information (PHI) for the uses listed below:

Information to be released by:	**Information to be released to:**
_____ (Name of health care provider, health plan, or health care clearing house) _____ _____ (Address) _____ _____ (Phone number)	[study investigator] (Name of person or organization) [institution name] (Address) (Phone number)

The information is released for the following uses:

ATSDR is asking providers to verify diagnosis or treatment of certain health conditions and outcomes for the named individual. ATSDR lists the conditions on the back of this form.

ATSDR will not ask for the release of PHI about alcohol or drug abuse treatment, genetics, and about reportable diseases, including sexually transmitted diseases and HIV-AIDS.

By signing below, I understand that:

- I do not have to sign this authorization.
- My authorization will automatically end at the end of the study; or
- I have the right to end my authorization at any time by writing a letter to this office.
- Ending my authorization will not affect any earlier release of PHI.
- Ending my authorization will not bar me from taking part in the study.
- Under my authorization, I have a right to look at or copy any release of PHI.
- I have a right to a copy of this authorization.
- No study reports will reveal my identity.

_____ **(Signature of Individual or Authorized Representative)** _____ **(Representative's Legal Authority to Individual)** _____ **(Today's Date)** _____ **(Phone Number)** _____ **(Date of Birth of Individual)**	_____ **(Print Name of Individual)** _____ **(Print Name of Authorized Representative)** _____ **(Address)** _____ |___|___|___| - |___|___| - |___|___|___|___| **(Social Security Number of Individual)**

The Privacy Rule issued under Health Insurance Portability and Accountability Act (HIPAA) is a regulation that provides protection for the privacy of certain individually identifiable health data ("protected health information"). HIPAA applies to covered entities, including health care providers who conduct electronic transactions, health plans (both public and private), and healthcare clearinghouses. CDC is generally not a covered entity; it is a public health authority. CDC/ATSDR may receive protected health information from covered entities, because CDC is a public health authority authorized by law to receive such information for public health purposes. Covered entities may, but are not required to, provide protected health information to CDC.

ATSDR or [institution name] may send a medical record abstraction form to be completed by the health care provider, health plan, or health care clearing house that you indicate on this form. Alternatively, ATSDR and NCEH staff or contractors may perform the medical record abstraction.

ATSDR and [institution name] are seeking information on the date of diagnosis or first treatment for the following health conditions (except as shown on Page 1). ATSDR and [institution name] are also seeking information if the individual is currently receiving treatment for these health conditions:

Diagnosis or Treatment of Health Conditions	***Adult***	***Child***
Osteoarthritis	√	--
Osteopenia and osteoporosis	√	--
Endometriosis	√	--
Heart Disease	√	--
Hypertension (including pregnancy-induced hypertension, preeclamsia)	√	√
Autoimmune diseases (including ulcerative colitis, rheumatoid arthritis, lupus, and multiple sclerosis)	√	√
Diabetes (including gestational diabetes)	√	√
Kidney Function (including kidney disease)	√	√
Lipid Disorder (including high cholesterol)	√	√
Thyroid Hormones	√	√
Liver Function (including liver disease)	√	√
Immune Response and Inflammation	√	√
Hypersensitivity-related outcomes (including asthma, atopic dermatitis/eczema)	--	√
Antibody responses to rubella, mumps, and diphtheria vaccines	--	√
Sex hormones, growth, and maturation	--	√
Neurodevelopmental outcomes (lower intelligence quotient (full scale IQ), attention-deficit, autism, and hyperactivity disorder (ADHD).	--	√
Parkinson disease	√	
Allergies	√	√
Infertility	√	