

**Agency for Toxic Substances and Disease Registry
(ATSDR)**

**“Human health effects of drinking water exposures
to per- and polyfluoroalkyl substances (PFAS)
at Pease International Tradeport, Portsmouth, NH”**

Pease Study – Proof of Concept

Manual of Procedures

November 9, 2018

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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 Pease Study Protocol 7161.0 was approved by the CDC Institutional Review Board (IRB) on 09/12/2018.
- 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).

2.0 Brief Overview of the Study Protocol

Per- and polyfluoroalkyl substances (PFAS) are a family of environmentally and biologically persistent chemicals used in industrial applications such as aqueous film-forming foam (AFFF), used to extinguish flammable liquid fires. Since the 1970s, military bases in the U.S. have used AFFF with PFAS constituents for firefighting training as well as to extinguish fires. At some military bases, AFFF use has resulted in the migration of PFAS chemicals through soils to ground water and/or surface water sources of drinking water for bases and/or surrounding communities. In 2016, the U.S. Environmental Protection Agency (USEPA) issued a lifetime health advisory level of 0.07 total micrograms of perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) combined per liter of drinking water ($\mu\text{g/L}$). In response to growing awareness of the extent of PFAS contamination across the U.S., Section 8006 of the Consolidated Appropriations Act of 2018 authorized the Agency for Toxic Substances and Disease Registry (ATSDR) to conduct a research study on the human health effects of PFAS contamination in drinking water.

In response, ATSDR is conducting the Pease Study, which will serve as a proof-of-concept model for a national multi-site study of PFAS health effects. The existence of a large body of state and local environmental monitoring and population blood testing data makes the Pease community in Portsmouth, NH, particularly suitable as ATSDR's initial PFAS research study site. From approximately 1970 until 1991, the Air Force used AFFF for firefighting and training at Pease Air Force Base. The base closed in 1991, and was converted to a large business and aviation industrial park in 1993, the Pease International Tradeport. In 2014, PFAS drinking water concentrations were detected (0.35 $\mu\text{g/L}$ PFOA and 2.4 $\mu\text{g/L}$ PFOS) at levels well above what was to become the USEPA lifetime health advisory level (0.07 $\mu\text{g/L}$ PFOA/PFOS). In 2015-7, the New Hampshire Department of Health and Human Services (NH DHHS) offered a PFAS blood testing program to the community. The blood testing program showed that

the Pease population had concentrations of some types of PFAS that were two to three times higher than national estimates.

The Pease Study will be cross-sectional in design, drawing from a convenience sample of people with and without exposure to PFAS-contaminated drinking water from Pease. The main goals of the study are to: 1) evaluate the study procedures and methods to identify any issues that need to be addressed before embarking on a national multi-site study; and 2) examine associations between health outcomes and measured and historically reconstructed serum levels of PFAS. ATSDR will examine the association between PFAS compounds and 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, ATSDR will investigate if PFAS is related to differences in sex hormones and sexual maturation, vaccine response, and neurobehavioral outcomes in children. In adults, additional outcomes of interest include cardiovascular disease, osteoarthritis, osteoporosis, endometriosis, and autoimmune disease.

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
 - ✓ 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. Outreach activities

ATSDR will work with NH DHHS and the Pease CAP to conduct outreach to encourage participation. The Pease CAP has offered to assist in recruitment of Pease and referent children and adults, and CAP involvement will be crucial in conducting outreach for the study. In advance of the start of the study, outreach will involve announcements to local elected officials, local media, community organizations, and the Portsmouth schools (Attachment 5). Outreach may also involve meetings with community representatives, medical societies, school officials, and/or public meetings. Although active in outreach, both NH DHHS and the Pease CAP will not directly obtain consent, intervene, or interact with research participants.

As part of the outreach, ATSDR will provide a factsheet to the Pease Development Authority (PDA) and Tenants Association of Pease Tradeport (TAP) so that it is included in newsletters and email notices to subscribing firms at the Pease Tradeport (Attachment 5, Attachment 7a&b, Attachment 9c). ATSDR and study investigators may request employers at Pease, PDA and TAP for rosters of current and former employees at the Pease Tradeport to assist with recruitment efforts. The study will also provide the factsheet to the Portsmouth schools, local media outlets, and to community organizations in Portsmouth (Attachment 5, Attachment 7d&e, Attachment 9c).

4.2 Screening and Eligibility Criteria

This section details the screening procedures outlined in the protocol to determine if an individual is eligible to participate in the study. If individuals must be enrolled in the study within a specific window of time following completion of the screening procedures, then such requirements should be included in the MOP.

Adults will be 18 years or older, and children will be 4-17 years of age at enrollment.

ATSDR will recruit, screen for eligibility, and enroll in three waves. The exposure group will be recruited in Waves One and Two. ATSDR estimates that 90 percent of the exposure group will be enrolled in Wave One (n=1,215), that is, will be past participants of the 2015-7 NH DHHS PFAS blood testing program. NH DHHS will assist ATSDR by sending out letters of invitation to its former blood testing program participants. To achieve the desired sample size, the other 10 percent of the exposure group (n=135) will be recruited in Wave Two. These will be people who were eligible for the PFAS blood testing program but did not take part. The referent group will be recruited in Wave Three (n=275), which can occur

concurrently with Wave One and Wave Two. Wave Two and Wave Three recruits will call to volunteer after ATSDR opens those waves to enrollment.

4.3. Recruitment strategies.

4.1.1 Wave One Recruitment from Biomonitoring Recruitment Frame

ATSDR will first recruit from those who participated in the NH DHHS Pease biomonitoring program in 2015-7. The NH DHHS, which manages the Pease biomonitoring records and possesses the recruitment frame for the Pease Study, will send out an introductory letter indicating its support for, and encouraging its former participants to contact ATSDR to take part in the ATSDR Pease Study (Attachments 6a&6b). The letter will provide a toll-free line that the interested person can call ATSDR to request participation in the study and/or ask any questions about the study. ATSDR will screen each interested caller using a Wave One eligibility screening script (Attachment 6c).

4.1.2 Wave Two Recruitment of Additional Exposed Children and Adults

Given that the Pease biomonitoring program recruited a convenience sample, no statistical sampling will be required. All biomonitoring participants in the recruitment frame will be recruited until the list is exhausted or until the required sample size is reached. If sample size requirements are not met in Wave One, ATSDR will further recruit individuals who were eligible but did not participate in the biomonitoring program. ATSDR will launch a media campaign to announce Wave Two (Attachment 5). A recruitment flyer will be sent to parents of other children identified as attending daycare centers at Pease before 2014 who didn't participate in biomonitoring in 2015-7 (Attachment 7a). Advertisement in local public media and through PDA and TAP would encourage other eligible adults to participate in the study (Attachment 5). The flyers will provide a toll-free number that interested recruits can call ATSDR to request participation in the study and ask any questions about the study (Attachment 7b). ATSDR will screen each interested caller using an eligibility screening script (Attachment 7c).

4.1.3 Wave Three Recruitment of Referent Children and Adults

For efficiency, Wave Three may occur concurrently with Waves One and Two. ATSDR will recruit a small referent group of 175 children and 100 adults not exposed to PFAS-contaminated drinking water. ATSDR will work with school officials to approve this school-based recruitment. ATSDR will also request that the schools distribute a flyer describing the study to students and instruct the students to give the flyer to their parents. Children will be recruited through outreach to Portsmouth schools and day care centers (for those 4-5 year old) (Attachment 7d). Recruitment of adult referents will include outreach to current adult education students among the five colleges at Pease (i.e., students who first attended these schools after closure of the Haven Well), Portsmouth government employees (AFSCME Local #1386), Portsmouth community organizations, and/or specific Portsmouth neighborhoods (Attachment 7e). ATSDR will screen each interested caller using an eligibility screening script (Attachment 7c). Both exposure and referent 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 8) to track recruitment success and to calculate non-response bias.

4.1.4. Recruitment Flow Diagram

An overview of the study processes, presented in a flow diagram in Figure 1, describes each of the study's major steps.

In total, ATSDR seeks to enroll 1,625 participants (1,100 adults and 525 children and their parents). ATSDR will not recruit by

5.0 Screening Log

A Screening log provides documentation of all individuals evaluated for study eligibility. It should include the identification number and individual's initials, age, gender, screening date, and eligibility status.

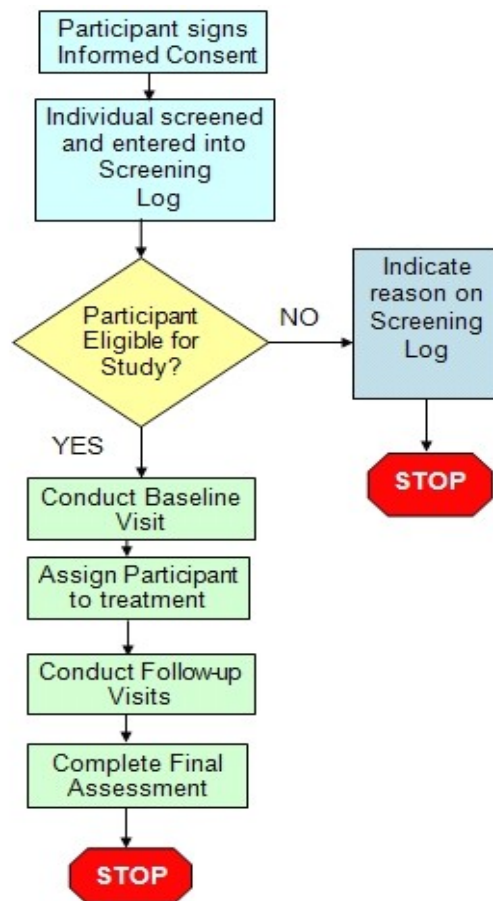
It may also contain the randomization number if different from the screening number. The MOP describes the contents of the Screening Log, specifically how data are entered, and processes for secure storage. A Sample Screening Log is available in [Appendix B](#).

Note: This information is usually part of the reporting requirements for data and safety monitoring.

5.1 Study Flow Diagram

An overview of the study processes, presented in a flow diagram in Figure 1, describes each of the study's major steps.

Figure 2: Study Flow Diagram



5.2 Eligibility Criteria

In total, ATSDR seeks to enroll 1,625 participants (1,100 adults and 525 children and their parents). ATSDR will not recruit by

For the exposure group (n=1,350), ATSDR will enroll 1,000 adults and 350 children. Eligible participants had to work at, live on, or attend childcare at the former Pease Air Force Base or the Pease International Tradeport, or live in a nearby home that was served by a PFAS-contaminated private well. Drinking water exposures must have occurred at some time between 2004 and May 2014, after which remediation of the public water supply occurred.

For the referent group (n=275), ATSDR will enroll 100 adults and 175 children. Eligible participants, never exposed to PFAS-contaminated drinking water from Pease, will come from other areas of Portsmouth, NH. Birth mothers of referent children likewise must never have had PFAS drinking water exposure.

To restrict this study to drinking water exposures, any adult occupationally exposed to PFAS will not be eligible for the study (i.e. ever firefighters or in chemical manufacture). Likewise, children whose birth mothers were occupationally exposed will not be eligible. This restriction applies to both the exposure and the referent group. ATSDR assumes that 5 percent of the people who volunteer will not meet eligibility requirements. ATSDR will screen 1,578 people from the NH DHHS PFAS blood testing program in Wave One. ATSDR will screen at least 142 exposed people in Wave Two, and at least 289 unexposed people in Wave Three. This will require an annual time burden of 124 hours for eligibility screening.

At enrollment, ATSDR will obtain adult consent, parental permission, and child assent before data collection begins. Each child will enroll with a parent, who ideally will be the child's birth mother, as ATSDR will ask details about the child's exposure, pregnancy, and breastfeeding history.

For each participant, ATSDR will take body measures, collect blood and urine samples for chemical and biomarker analysis, and administer a questionnaire on exposures and medical history. ATSDR assumes that 20 percent of parents will also enroll as adults; therefore, 420 parents will take the child questionnaire long form, while 105 parents will take the short form to reduce burden. Parents and children will also complete assessments of the child's attention and behaviors.

ATSDR will ask for permission to compare adults' and children's medical histories with their medical records. ATSDR will also ask for permission to check children's school records to compare their behavioral assessment results.

5.3 Informed Consent (see Section 11.3.)

Detailed instruction on administering an informed consent package are outlined in the section 11.3; briefly general:

- Consent will be obtained at the study office before any data collection commence
- Study interviewers as directed by the study manager/coordinator will discuss the nature of the study with the individual and sign the consent form

- A copy of the signed consent will be given to the individual after the signing and the original signed copy of the consent be stored will be stored in the study office
- *Re-consent process, if individuals need to be re-consented at any part of the study.*

The CDC IRB approved Informed Consent form is included as an appendix in the MOP.

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.

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 Experiences chest pain	Nurse will: CALL 911 and notify other health personnel in the building.

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	
<i>Name</i>				
<i>Address</i> <i>Phone</i>		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/oas/os/hrpo/guides/4-incidents-v1.1.pdf>]

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](#).

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 Plane 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?”

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.

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
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 stylyus (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 staff 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:

Table 1. Classification of blood pressure in adults aged 18 years or older.

BP Category	SBP (mm Hg)		DBP (mm Hg)	Action*
Normal	<120	And	<80	no referral
Prehypertension	120-139	Or	80-89	no referral
Hypertension	140-159	or	90-99	See a physician within 2 months for recheck
	≥ 160	or	100	See a physician within 1 month for recheck
	≥180	Or	≥110	Immediately

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.

10.0. Blood Sample Collection, Processing and Shipping Protocol

Venipuncture should be performed in the fasting state after blood pressure measurement. In adults, **30 ml** of blood shall be collected to recover and about 11 ml of sera for the analyses of PFAS and clinical and other effects biomarkers, as well as 2ml of whole blood for the analyses of glycated hemoglobin and whole blood reserve. In children, **20 ml** of blood shall be collected to cover 2 ml of whole blood and about 9 ml of serum for PFAS and clinical and other effects biomarkers (See Attachment 3 for details).

The volumes to be collected can be adjusted once a commercial laboratory is 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
- Three 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:

- Refrigerator and -30°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 three (two for children) 10 mL red top serum tubes**
7. Push purple top tube into the needle holder.
8. **Collect two EDTA purple top tubes**
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.
15. 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 too 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.

- o 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)**
- **Fifteen (15) 2 mL cryovials (CDC)**
- Bar-coded labels CDC
- Centrifuge (CDC)

- Freezer (**Contractor**)

2. Processing

- 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 tube 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
8	CK-18 (M60, M35)	1.0 ml serum	Yes	Yes	Commercial Lab
9	Immune function (Immunoglobulins)	1.0 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	2.0 ml serum	No	Yes	Commercial

	parameters				Lab
	[Total Serum needed for planned clinical and effect biomarkers analyses]		9 ml	11 ml	
14-15	Any reserve or excess serum	1 ml aliquots	--	--	CDC

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.

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.

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



- 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.	

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

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, any excess serum aliquots, and 15 ml urine aliquot (see section 10.5) will be assigned and labeled with CDC Unique Identifier CUID (required in addition to sample identifier) by the sample logistic team and transferred from Chamblee campus (NCEH/DLS) to the CDC biorepository facility for storage. The contact person for the CD biorepository 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 (100 ml?), urine collection instructions (see Steps below), gloves, insulated cooler, and ice pack, which they'll be instructed to store in their freezer.

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. Study staff will pipette 15 mL of urine into a centrifuge tube.

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. Please study staff will pipette 15 mL of urine into a falcon tube for future creatinine or specific gravity analyses.

For urine samples for future PFAS analysis, contractor will pipette 1.8 mL of urine for the collection container into a cryovial and ship samples overnight on dry ice from the bio-specimen repository to the NCEH laboratory in Atlanta, Georgia. Study staff and NCEH/ATSDR personnel will maintain and manage proper chain of custody for all urine samples.

Centrifuge (Falcon) tubes 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. Please 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 biospecimen 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 selected for laboratory analysis will be stored at CDC DLS and CDC biorepository (see section 10.4) as needed for future analyses of 18 PFAS and creatinine/specific gravity. Additional analytes may be added should methods become available.

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.

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. HIPPA 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
 - b. Bag
 - c. CDC laptop, Charged

paper forms

- 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

- 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 signs 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)
- 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. Record the Start Time
3. Ask ALL questions as appropriate.
4. Record the Stop Time

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.

Example:

6-1.	Would you say that in general your health is excellent, very good, good, fair or poor?
1	EXCELLENT
2	VERY GOOD
3	GOOD
4	FAIR
5	POOR

8	DK/NS
9	REF

If the respondent had answered that he or she generally felt “good” the interviewer would circle the number 3 next to the Good 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:

12-2. Which one of these groups would you say best represents your race? Would you say White, Black or African American, Asian, American Indian, or another race?

1	WHITE
2	BLACK OR AFRICAN AMERICAN
3	ASIAN
4	AMERICAN INDIAN
7	OTHER: Please specify _____
8	DK
9	REF

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

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:

7-1. What is your age?

____ _ YEARS OF AGE

8	DK
9	REF

Example of Height:

H52. About how tall are you without shoes?

_____ Record height in feet and inches (For example, 501 = 5 feet, 1 inch)

998 DK/NS

999 REF

Example of Frequency:

H44. How often do you drink fruit juices such as orange, grapefruit, or tomato?

1 _____ TIMES PER DAY

2 _____ TIMES PER WEEK

3 _____ TIMES PER MONTH

98 DK

99 REF

In these cases, a participant's answer may be given in terms of days, weeks, months, or years. The interviewer must choose the correct time unit and fill in the spaces beside it. For example, if someone responded with "3 times a week" the interviewer would write "03" in the blanks next to the "per week" response. This format allows answers to be recorded easily and precisely. The respondent may give an answer that should be converted to fit one of the time units given. For example, if the respondent answers "once every two weeks" convert this to months and record the answer as "02" in the blanks next to the "per month" response.

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

5. Open-ended Questions

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:

11-6. Please describe those negative health effects?

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 / not sure ("DK/NS").

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 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.

1. Normal Text

Text written in a normal font is read to the respondent. This includes questions, response codes, and transition statements. However, it is not necessary to read the question numbers.

2. Bold Text

Text written in **bold font** is NOT to be read to the respondent. Most response categories are in bold text and are not to be read to the respondent. The only exception is if the respondent needs to hear the categories to make an accurate decision.

3. Italicized Text

Text written in *italicized font* is NOT to be read to the respondent. Italics are used for instructions to the interviewer for how to move through the questionnaire or how to record responses.

4. All Capitalized Text

Text written in CAPITALIZED FONT is NOT to be read to the respondent. All capitals are used to mark questionnaire sections, recording the respondent's gender, and for DK/NS & REF response categories.

Examples:

Not Read	<u>SECTION 2: DIABETES</u>	
Read	These next questions ask about your diabetes.	
Read	2-1.Are you now taking insulin.	
Not Read	1	YES
Not Read	2	NO
Not Read	8	DK
Not Read	9	REF

Read	7.17. How long has it been since you had your last mammogram?	
Not Read	READ ONLY IF NECESSARY	
	1	Within the past year (<i>Anytime less than 12 months ago</i>)
	2	Within the past 2 years (<i>1 year but less than 2 years ago</i>)
	3	Within the past 3 years (<i>2 years but less than 3 years ago</i>)
	4	Within the past 2 years (<i>3 years but less than 5 years ago</i>)
	5	5 or more years ago
	6	DK
	7	REF

Not Read	INDICATE SEX OF RESPONDENT	
Not Read	1	MALE
Not Read	2	FEMALE

Read	12-6. Is your annual household income from all sources?
------	---

	01	Less than \$10,000?
Read	02	Less than \$15,000?
Read	03	Less than \$20,000?
Read	04	Less than \$25,000?
Read	05	Less than \$35,000?
Read	06	Less than \$50,000?
Read	07	Less than \$75,000?
Read	08	\$75,000 or more?
Not Read	98	DK/NS
Not Read	99	REF

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.

6. Nested Questions

A nested question is one that contains a common question stem and several statements that follow having the same response categories. For these questions, read the question stem first, then ask each statement one at a time recording the response for each statement before moving on to the next one. Continue until all statements have been read.

Example:

Sec 1. The first set of questions asks about different health conditions. Has a doctor ever told you that you had

	<u>Yes</u>	<u>No</u>	<u>DK/NS</u>	<u>REF</u>
1-1. Cancer	1	2	8	9
1-2. Stroke	1	2	8	9
1-3. Liver Disease . . .	1	2	8	9
1-4. Kidney Disease. . .	1	2	8	9

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).

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 CATI area of the *Survey Research Unit* is supervised, and all calls are recorded.

With regards to on and off-site interviewing - The CATI 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.

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 and management of data

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

The study staff-contractor will collect, 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 Pease Study will be cross-sectional in design, drawing from a convenience sample of people with and without exposure to PFAS-contaminated drinking water from Pease.

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, medical 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.

ATSDR needs up-to-date PII for the informed consent process and to send participants' study results. ATSDR will use PII to report 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 Pease 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 collect 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), developing data collection forms, and administering the data collection. ATSDR will collect information in several modes: (1) hardcopy and then 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 also transfer the data via VPN/CITGO to the designated encrypted CDC/ATSDR MUST share. All collected data will be transferred daily to CDC and laptops data deleted by the contractor. 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

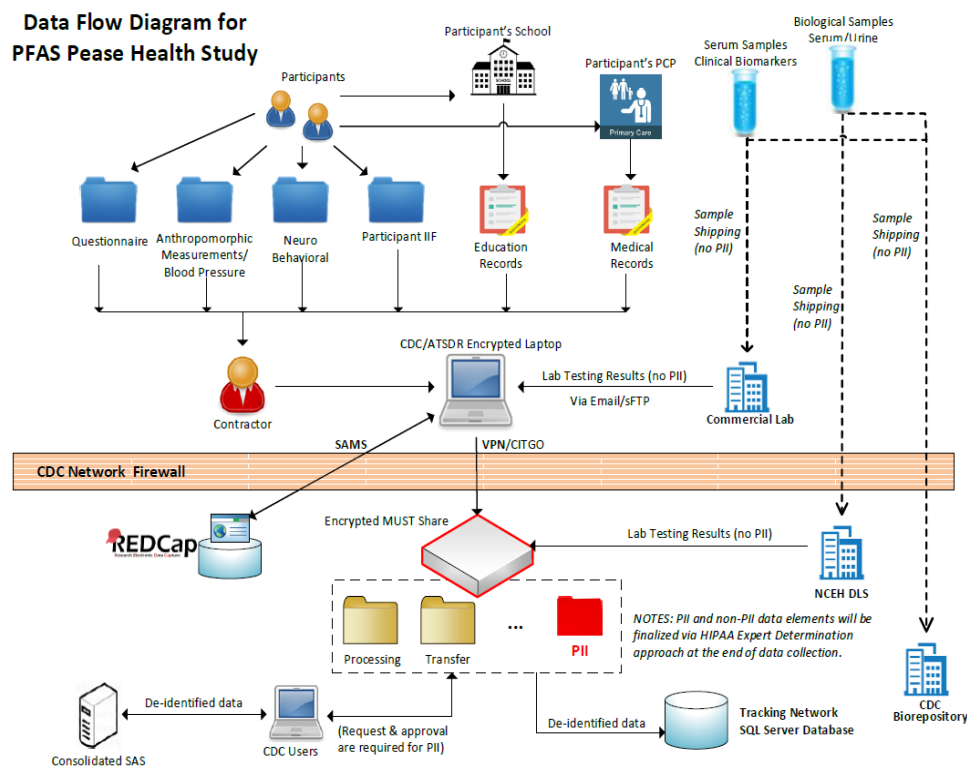
Contractor' study staff will follow checks and quality control procedures for data entry. Only authorized study staff will receive permission to enter or manipulate the study data. Data entry from hardcopy documents will involve double entry with discrepancies compared and corrected or will be scanned and transferred using ATSDR approved devices and methods (refer to the data flow diagram for details).

Study staff will prepare draft datasets to record questionnaire responses and medical record/school record data to send to ATSDR for review and approval. 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.



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
- 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 via access to encrypted share drive at CDC. 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 access activities (including information as users, storing location, duration, etc.) to PII will be required.

13.1c Access Controls and Security

Per the Pease 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.*

The study staff will provide details on its data security technology and methods including password protection, desktop firewalls, daily backups and server based storage, intrusion detection, vulnerability scans of personal computers and server, laptop security, and computer encryption procedures.

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.

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.

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

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
- 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.

13.4. Encrypted Multi-User Share Tool (MUST)

Share Location (URI): \\cdc.gov\locker\ATSDR_Pease_PFAS_Stu.

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
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\locker\ <STUDY NAME>	Share Root	<STUDY NAME>-FC	Full Control (FC) - read, write	Admin
\\cdc\locker\ <STUDY NAME>	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 Subfolder	<STUDY NAME>.Raw_Data-ro	Read Only (RO) - read	General 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 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
- 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
- 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)

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

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

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.

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 Pease CAP of study results published in peer reviewed publication(s) by study staff.

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](#).

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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/cfcr/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>

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	<input type="checkbox"/> M <input type="checkbox"/> F	// mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	// mm/dd/yyyy
□□□□	// mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	// mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	// mm/dd/yyyy
□□□□	// mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	// mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	// mm/dd/yyyy
□□□□	// mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	// mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	// mm/dd/yyyy
□□□□	// mm/dd/yyyy	<input type="checkbox"/> M <input type="checkbox"/> F	// mm/dd/yyyy		<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> 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.