Supporting Statement B for Request for Clearance

Developmental Projects to Improve the National Health and Nutrition Examination Survey And Similar Programs

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Dual Energy X-ray Absorptiometry (DXA) and Hematology Analyzer and Blood Collection Tube Crossover Studies

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1. Respondent Universe and Sampling Methods

In 1999, NHANES became a continuous ongoing survey to provide more timely data on the health and nutritional status of the U.S. population and to allow more flexibility in response to the need for data to address emerging public health concerns. From 1999 to 2018, NHANES used multiyear sample designs with varied lengths for 2-year data collection and release cycles. Because of the COVID-19 pandemic, the NHANES 2019–2020 data collection could not be completed. In August 2021, NHANES went back into the field with a newly designed 2-year cycle, which ended in August 2023. During this cycle, only minors (i.e., 0-19 years) and older people (60+) were oversampled, and there was no oversampling for any racial/ethnic group.

The 2025-2026 NHANES design remains a stratified, multistage probability sample of the civilian non-institutionalized population of the United States. In hierarchical order, the stages of the sample selection are first: selection of Primary Sampling Units (PSUs) (public use microdata areas [PUMAs]); second: Secondary Sampling Units (SSUs) within PSU (Census block groups [CBGs] or a collection of CBGs containing a cluster of DUs [dwelling units]); third: DUs within SSUs; and fourth: one or more survey participants within DUs. The field operations include five Mobile Examination Center (MEC) teams in operation and approximately 5,000 survey participants examined in 20 PSUs per year compared to 15 PSUs per year in the August 2021-August 2023 NHANES cycle. For the 2025-2026 cycle, NHANES will oversample children 0-17 years of age, older persons age 65 and older, and non-Hispanic Black persons.

DHNES proposes two crossover studies with human subjects (i.e., volunteers) recruited by RTI International (i.e., DHNES contractor) to assess the impact of using 1) a new Dual Energy X-ray Absorptiometry (DXA) densitometer system among 30 participants ages 20-70, and 2) a new Hematology Analyzer among 40 participants age 20 and older. Additionally, the reliability and reproducibility of NHANES lab test results from different source tubes will be assessed in the hematology study. While the proposed crossovers are described separately, both studies will be conducted concurrently outside of the main NHANES study design using the same volunteers. These projects are submitted as one GenIC under the previously approved Developmental Projects to Improve the National Health and Nutrition Examination Survey and Similar Programs (OMB No. 0920-1208, Exp. Date 05/31/26) generic clearance. Results from both crossover studies will allow DHNES to assess new methodologies prior to the start of the 2025-2026 cycle.

2. Procedures for the Collection of Information

Dual Energy X-ray Absorptiometry (DXA) Crossover Study

As previously mentioned in Supporting Statement A, for the DXA crossover study, RTI International will lead recruitment efforts of a convenience sample of 30 volunteers from

the area where the study will take place (i.e., USDA campus in Maryland) in the Fall of 2024. A recruiting agency identified by RTI International will share the following information for recruiting the volunteers:

- This is for a health study being conducted by the Department of Health and Human Services.
- Volunteers are needed for 1 hour (with date and time of appointment).
- Volunteers will get a total 6 DXA scans that look at bone density and body composition.

Recruiting will be based on gender and age. A set of screening questions will be asked over the telephone with interested potential participants. The screening questions include age, gender, primary spoken language, and additional exclusion questions to ensure they will be able to complete the whole body, spine, and femur scans (see **Attachment 1**).

After providing consent (see **Attachments 2a and 2c**), participants will complete three DXA scans (whole body, spine, and femur) on the Hologic Horizon A Fan Beam Bone Densitometer (SN 301832M). Then participants will receive the same three scans using the new Hologic Horizon A Fan Beam Bone Densitometer. All scans will be taken with participants laying on their backs. All scans will be administered by the DXA consultant contractor from the University of Hawaii (UH), who holds a radiology certification from the American Registry of Radiologic Technologists (ARRT). The ARRT certification is recognized in all 50 states. During the study, one DHNES physician will be present in MEC as well. The DXA consultant has extensive experience with DXA systems and for the past 9 years has been training radiology technologists for DHNES.

The DXA images will be transferred from the Hologic computer to an RTI laptop with a secured environment via an encrypted USB drive. UH collaborators will only access and analyze the images using the RTI laptop and will lose access once correction factors are calculated during analysis. No image will be stored on the Hologic computer and once the analysis is completed using the secured RTI laptop, the original and analyzed scans will only be stored on the NCHS server, indefinitely, in case there is a need for future calculations.

A urine sample will be collected from people who were born female and are of childbearing age (20-59 years old). A urine pregnancy test will be performed in the MEC to determine pregnancy status. A certified medical laboratory scientist will perform the pregnancy test. Urine pregnancy test results will be reported to participants. Females of childbearing age will be excluded from the study if their urine pregnancy test is positive, if they say they are pregnant, or if they decline to take the pregnancy test.

NHANES will provide a cover letter and report of findings (**Attachment 3**) containing the following results to the volunteers prior to leaving the MEC (Note: The cover letter and report of findings are provided to participants for participation in the DXA and/or Hematology Analyzer Blood Tube studies):

- Total body fat percent;

- Hip and spine bone mineral density (BMD) with interpretations using T-scores; and
- Urine pregnancy results (when applicable).

Hematology Analyzer and Blood Collection Tube Comparison Study

Part 1: Hematology Analyzer comparison study

This comparison study will be conducted by recruiting 40 volunteers age 20 and older using the same recruitment strategy proposed for the DXA crossover study. As previously mentioned in Supporting Statement A, a venipuncture will be performed to obtain two Ethylenediaminetetraacetic acid (EDTA) lavender blood tubes of 4ml each. Volunteers' blood will be analyzed on both the new (DxH560) and the current Coulter (DxH800) systems simultaneously. The results will be analyzed by the DHNES Method Validation Team to determine if the results are comparable or are statistically different. The testing lab will be instructed to destroy all samples and sign a destruction form 30 days after the DHNES Method Validation Team completes their analysis.

Part 2: Blood Collection Tube Type comparison study

The same convenience sample of 40 volunteers recruited for Part 1 of the hematology study will participate in Part 2, where the results of the biochemistry panel, C-Reactive Protein (CRP), insulin, and Per- and polyfluoroalkyl (PFAS) tests using Red Top Tubes will be compared to results using SSTs to verify data consistency between collection tube types. As previously mentioned, this study will inform DHNES if SSTs are a feasible option to reduce processing time and maintain sample quality.

Volunteers who meet any of the following criteria are not eligible for either the CBC component (i.e., Part 1) or tube study (i.e., Part 2):

- Hemophilia; and
- Cancer chemotherapy within last 4 weeks
- Non-English speaking
- Any condition for which the MEC physician deems to put the participant at significant risk.

The recruiting agency identified by RTI International will share the following information for recruiting the volunteers:

- This is for a health study being conducted by the Department of Health and Human Services.
- Volunteers are needed for 10 minutes (with date and time of appointments).
- Volunteers will get a total of 4 tubes drawn.
- The study will be conducted at the USDA campus in Beltsville, MD

Please see **Attachment 1** for a description of the hematology study and eligibility phone screening questionnaire administered to potential volunteers. Informed consent will be obtained for the hematology study upon participant's arrival to the MEC after reading

and reviewing the attached form (**Attachment 2b**). Participants who agree to participate in both the DXA and hematology crossovers will provide consent using a separate form (**Attachment 2c**).

Safe blood draw limits were verified using the World Health Organization's safe blood draw limits. We determined the minimum weight in kilograms from several NHANES cycles to determine the amount of blood being drawn was less than 5% of total blood volume (TBV). Each volunteer will go through a venipuncture to collect a total of four tubes. Part 1 requires two 4mL EDTA tubes and Part 2 requires one 10mL Red Top tube and one 8.5mL SST. Total blood drawn, including both Parts 1 and 2, is 26.5mL of blood, which is equivalent to 0.90 ounces or 1.8 tablespoons.

Venipuncture will be performed primarily using the median cubital vein at the elbow. The DHNES Lab Team staff, which consists of two Medical Laboratory Scientists (MLS), will instruct the volunteer to sit in the phlebotomy chair and prepare them for venipuncture. The MLS will inspect the volunteer's arm, apply a tourniquet several inches above the selected site. The applied tourniquet will not be in position for more than one minute while searching for a vein. Next, the MLS will reapply the tourniquet to prepare the site for the venipuncture, by cleansing the site with an alcohol wipe using a scrubbing back and forth motion and wait for the cleansed area to dry. The MLS will perform the venipuncture and fill four blood tubes. When the last tube is filled, the tourniquet will be removed followed by the needle in a smooth quick motion avoiding heavy pressure. The MLS will discard the entire blood collection set, including needle and adapter, into a biohazard sharps container. The MLS will check the venipuncture site for clotting. The MLS will apply a CoFlex dressing over the gauze pad and instruct the volunteer to remove the bandage no less than 45 minutes from the completion of the procedure if bleeding has stopped.

CBC results from DxH800 will be reported to volunteers before leaving the MEC. Additionally, a second report of findings will be mailed to the participants within three weeks of their appointment for the biochemistry panel. Reported results sent to volunteers are from a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. CLIA requires any facility performing examination to be certified. As described in Part 1 of this study, all samples will be destroyed by the testing laboratory 30 days after the data has been analyzed by the DHNES Method Validation Team. In all cases, volunteers can refuse to receive any or all test results by informing the MLS or contacting the DHNES Chief Medical Officer (CMO).

Following what has been approved in the NHANES main study, the following tests will not be reported in the report of findings: hs-CRP, insulin, or PFAS. Any form of hs-CRP has limited clinical significance if not interpreted alongside other variables, the result of this test is not reported. Insulin levels are used to assess the body’s ability to regulate blood sugar and to aid in the diagnoses of insulin resistance, prediabetes, and type 2 diabetes. However, the clinical significance of these levels is not yet known, thus, results will not be reported. PFAS does not have an established threshold that can be used to

define health effects; thus, the measurement cannot be interpreted and thus are not clinically actionable and will not be reported.

For each reported result, specific language has been prescribed to present an interpretation of the finding, provide relevant information and, if appropriate, recommend further medical evaluation. All test results clearly emphasize "These measurements were obtained as part of a study to test accuracy of laboratory equipment and do not represent a medical diagnosis. Interpretation of these results must be made by an appropriately licensed healthcare provider." Further, any test results that includes laboratory results will include laboratory information detailing where each test was run.

When volunteers are notified of an abnormal result, they may be encouraged to seek further medical evaluation. The specific process will vary based on the potential severity of the abnormal result and when it is discovered, as outlined below.

- For abnormal CBC results identified in the MEC, the MLS will inform DHNES CMO so they can:
    - counsel the volunteer regarding the abnormal reportable result,
    - provide the volunteer with a written report detailing the result (in the Report of Findings – see **Attachment 3**), and
    - provide recommendations that may include following up with their healthcare provider (as applicable).

  The volunteer will also receive a cover sheet that states they should follow up with their medical providers for any questions or abnormal results (see **Attachment 3**). The cover letter will also have contact information for the DHNES CMO if the evaluating provider requires additional information.

- Abnormal results identified by the laboratory running the test.
  During the analysis of the tube study, abnormal results that have immediate impact on the health of the volunteer may be identified. Based on reference ranges set by the lab assay, the appropriate reference ranges are set within the Laboratory Information Management System (LIMS). The testing laboratories transmit results once they are available, to be uploaded on the NHANES secure File Transfer Protocol site where abnormal results will be flagged. For any immediate clinically concerning results, the DHNES CMO will be made aware via alerts sent from Subject Matter Experts (SMEs) at the testing laboratories who are assigned to review these data. All results (both normal and abnormal) will be mailed out in the second report of findings within 21 days of the labs receiving the samples. This is consistent with the NHANES main study of sending "Early Reports" for results that may be more clinically urgent.

NHANES volunteers can speak to the DHNES CMO (or if unavailable, another DHNES medical officer) regarding questions about results from their test results by calling a toll-free telephone number, 1-800-452-6115, during regularly scheduled business hours, Monday–Friday, 9 am–5 pm Eastern Time.

The results from hematology analyzer and tube studies for the volunteers will be contained within a restricted Excel file accessed only by the NHANES study team working on this project. Copies of the signed consent documents will be stored in a secure, locked file cabinet. Documents will be shredded at the conclusion of the study. There are no plans to publish the results of this two-part study at any conference or in any journal.

RTI International is responsible for data collection procedures for these crossover studies. The responsibilities of the contractor will be:

- Identify local recruiting agency,
- Recruit participants via the phone and administer the screening questions,
- Set up, conduct, and maintain data collection activities,
- Greet and check participant into the crossover when they arrive,
- Collect and secure volunteer data, and
- Check out and pay remuneration when participant is done.

3. Methods to Maximize Response Rates and Deal with Nonresponse

RTI will work with recruiting agency to continually advertise until all cells have reached minimum size.

Other methods to maximize response in these crossover studies include:

- Remuneration to help cover out of pocket expenses such as travel or childcare;
- Allow a companion (parent, caregiver, etc.) to accompany participant;
- Provide a report of examination findings;
- Flexible appointment schedule;
- Telephone and text reminders before scheduled appointments; and
- Customized follow-up efforts.

4. Tests of Procedures or Methods to be Undertaken

DXA studies
Comparisons using the scans between the old and new systems will be undertaken in the DXA crossover study. Using a Deming regression, conversion equations will be derived. These equations will be used to calibrate the new system so DXA comparisons over time can be made.

Hematology studies
The results from both parts of the Hematology Comparison Study will be analyzed using a correlation plot with regression analysis. Plots will be examined for outliers and

outliers will be excluded. Outliers will be determined using an assumption of normal distribution, results greater than 3 standard deviations from the mean will be flagged for follow-up. Further investigation of the measurement process will determine the outlier to be true or not. True outliers will be removed from analysis. Regression, summary statistics, and 95% confidence intervals will be calculated. Results will be reviewed with the NHANES method validation team to determine appropriate next steps.

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

1) The following person was consulted in the statistical aspects of the design of this project:

Te-Ching Chen, PhD
Mathematical Statistician
Division of the National Health and Nutrition Examination Surveys
National Center for Health Statistics
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2) The following person is responsible for the data collection activities:

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3) The following person is responsible for the analysis of this data:

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