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PATH Study Biospecimen Access -
Policies and Procedures for Investigators

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1 PATH Study Biospecimen Access Program

The Population Assessment of Tobacco and Health (PATH) Study Biospecimen Access Program (BAP) provides independent investigators with access to the biospecimens collected from PATH Study participants. Investigators proposing meritorious and feasible studies consistent with the PATH Study objectives and/or research priorities in tobacco regulatory science will be given highest priority for access to these biospecimens. Studies that address other objectives, which advance the knowledge of tobacco use and/or tobacco-related health outcomes will also be considered.

1.1 Purpose of This Document

This document (PATH Study Biospecimen Access – Policies and Procedures for Investigators) was developed for independent investigators who wish to use PATH Study biospecimens in their own research studies. It describes the PATH Study Biospecimen Access Program, informs investigators of PATH Study policies for obtaining biospecimens, and provides step-by-step instructions for the application process. The document also provides information on other PATH Study resources that are available including questionnaire and biomarker data.

1.2 The PATH Study Team

The PATH Study team, comprised of staff from the National Institute on Drug Abuse (NIDA), National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA) Center for Tobacco Products (CTP), Westat, and Fisher BioServices, is responsible for administering the Biospecimen Access Program. The groups and their roles and responsibilities are described below:

- **The Biospecimen Access Committee (BAC):** The BAC has the primary responsibility for reviewing requests for biospecimens submitted by independent researchers. This includes reviewing concept statements and applications. The BAC makes recommendations to PATH Study management on which applications to support. The BAC also reviews appeals to overturn denied applications and PATH Study addendums, and makes recommendations on these requests to PATH Study management.

  The BAC is composed of standing members drawn from the PATH Study Biospecimen Access Program who have expertise in biospecimen and laboratory sciences, tobacco research, and tobacco policy and regulation. The BAC will invite ad hoc subject matter experts as needed.

- **PATH Study Management:** PATH Study management comprises Program Officials within CTP and NIDA. This group is responsible for making final decisions on which applications to support.
Westat: Under a contract with NIDA, Westat implements and monitors the PATH Study Biospecimen Access Program activities.

Fisher BioServices: Fisher BioServices is the biorepository for the PATH Study. The repository staff pull biospecimens from storage, and pack and ship them to investigators’ laboratories to fulfill approved applications.

1.2.1 Communication with the PATH Study Team

Investigators should direct all questions about the PATH Study Biospecimen Access Program and the policies and procedures for accessing biospecimens to the PATH Study team at the following e-mail address: PATHStudyBiospecimens@westat.com. The PATH Study team will respond to questions, send requests and notifications, and as needed, provide documents to investigators from this e-mail address.

2 PATH Study Resources Available to Investigators

The PATH Study is a national cohort study designed to generate longitudinal epidemiologic data on tobacco use behaviors including patterns of use, attitudes, beliefs, exposures, and related health conditions of the U.S. population. The cohort is a household-based, nationally representative sample of approximately 46,000 participants. These include both youth (12 to 17 years) and adult (18 years and older) users and nonusers of a wide array of tobacco products. Both biospecimens and data are collected from PATH Study participants over time, in annual and biennial waves. The PATH Study and its participants are described in more detail in Appendix A. Investigators can also refer to Hyland et al., Design and methods of the Population Assessment of Tobacco and Health (PATH) Study in Tobacco Control 2017;26(4):371-378.

Documentation for the PATH Study and investigator access to questionnaire and biomarker data is available on the University of Michigan’s National Addiction & HIV Data Archive Program (NAHDAP) website. The following NAHDAP website pages are useful to investigators wishing to access PATH Study biospecimens and data:

- PATH Study Series – Access all documentation and study data starting from this page.
- PATH Study Restricted-Use Files (RUF) – Access a description of the PATH Study, publications, questionnaires, codebooks and apply to access RUF questionnaire data.
  - Download the RUF User Guide
- PATH Study Public-Use Files (PUF) - Access a description of the PATH Study, publications, questionnaires, codebooks and download PUF questionnaire data and documentation.
- Download the PUF User Guide

- PATH Study Biomarker RUF – Access documentation about available biomarker data, codebooks, biospecimen procedures, laboratory methods and apply to access the biomarker RUF.
  - Download the Biomarker RUF User Guide

- PATH Study Biospecimen Access Program – Access a description of the Biospecimen Access program and instructions on how to apply to access PATH Study biospecimens.
  - Read How to Apply for Biospecimens

## 2.1 Biospecimens

Biospecimens (urine, blood, and buccal cells) are collected from consenting PATH Study participants under a protocol reviewed and approved by the Westat Institutional Review Board (IRB) using validated PATH Study standard operating procedures (SOPs). In Wave 1, all three types of biospecimens were collected from adult participants; however, buccal cells were only collected during the first eight months of Wave 1. In Waves 2, 3, and 4 serial urine specimens are collected from adult participants who gave urine in a previous wave, and blood and urine are collected from participants who turned 18 years old during the respective wave year. Collection of additional serial urine specimens from adults is planned for Waves 5, 6 and 7. Collection of serial blood specimens from adults who gave blood in Wave 1 is planned for Wave 6. No biospecimens were collected from youth participants until Wave 4, when urine was collected, followed by planned collection of serial urine samples in Waves 5, 6 and 7. The types of biospecimens collected and planned collection(s) at each wave are presented in Table 1.

<table>
<thead>
<tr>
<th>Collection Wave</th>
<th>Annual</th>
<th>Biennial</th>
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<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adult Urine</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Youth Urine</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Adult Blood</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Adult Buccal Cells¹</td>
<td>✓</td>
<td></td>
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✓ Current serial specimen collection
✓ Planned serial specimen collection

¹ Due to competing priorities and limited funding, buccal cells were collected only during part of Wave 1 (September 12, 2013 through May 18, 2014).
Biospecimens are shipped from the field to the PATH Study biorepository and processed into the following components:

- Urine aliquots (no preservative);
- Plasma aliquots (EDTA);
- Plasma aliquots (citrate);
- Serum aliquots (no preservative);
- Genomic DNA (gDNA) aliquots isolated from buffy coats (EDTA);
- Red Blood Cells fraction aliquots (EDTA); and
- PAXgene blood RNA tube.

Additional documentation on the procedures for collecting, processing, and storing PATH Study biospecimens can be found on the PATH Study Biomarker RUF page.

### 2.1.1 Currently Available Biospecimens

Currently, urine, serum, plasma (EDTA), and gDNA biospecimens collected during Wave 1 are available to investigators under the PATH Study Biospecimen Access Program. Biospecimens from subsequent waves will be available at a future date and announcements for their availability will be posted on the PATH Study Biospecimen Access Program page.

### 2.1.2 Quantity Limitations

Applicants must justify the quantity of the biospecimens requested for their proposed study. Due to the limited quantity of biospecimens collected from PATH Study participants, it may not be possible to approve requests which exceed the following:

- Urine – 1.0 mL
- Serum – 200 uL
- Plasma (EDTA) – 200 uL
- gDNA – 50 ul at a concentration of 25 ng/ul

### 2.2 Biomarker Data

Wave 1 urine, serum, and plasma specimens from subsamples of PATH Study participants (n =11,522 for urine; n=7,159 for serum and plasma) were analyzed for biomarkers of potential harm and tobacco exposure by the Centers for Disease Control and Prevention (CDC), Division of Laboratory Sciences and GenWay BioTech, Inc. Each subsample of participants with biomarker
data includes tobacco product nonusers as well as a diverse mix of tobacco product users. The latter includes exclusive current cigarette users, current users of other tobacco products, experimental only users of any tobacco product, and former users of tobacco products. The list of biomarkers analyzed can be accessed from the PATH Study Biomarker RUF page. The results of the biomarker analyses are available in the biomarker RUF.

2.3 Biospecimens from Participants with Biomarker Data

Investigators can request biospecimens from participants who have linked biomarker data, if the biomarker data are needed to meet their study aims. The numbers of Wave 1 adults who have biospecimens and the subsamples of these adults who also have biomarker data, categorized by tobacco product user group, are provided in Table 2 on PATH Study Biospecimen Access Program page. Investigators should review this table when designing their studies to ensure there are sufficient participants with both biospecimens and biomarker data in the desired tobacco product user groups.

2.4 Questionnaire Data

Data are collected from PATH Study participants during each wave about the types of tobacco product used, tobacco behaviors (use, cessation, relapse, and transitions between products), exposures, attitudes, beliefs, knowledge, and health using comprehensive questionnaires designed specifically for youths 12 to 17 years old (Youth Questionnaire) and adults 18 years and older (Adult Questionnaire). The questionnaires are self-administered using Audio Computer-Assisted Self-Interviewing (ACASI). The questionnaires incorporate unique ACASI features such as the inclusion of images of tobacco products to help respondents identify which products they use and extensive use of tailored question wording based on responses to previous items. The questionnaire data are available in both the PUF and the RUF.

2.5 Accessing Questionnaire and Biomarker Data

As indicated above, questionnaire data are available in the PUF and RUF. Biomarker data are available only in the biomarker RUF. Questionnaire data in the PUF may be downloaded directly from the PATH Study PUF page. Investigators who wish to access questionnaire data in the RUF and/or biomarker data in the biomarker RUF must complete an application through NAHDAP at the PATH Study RUF page or the PATH Study Biomarker RUF page.

Investigators should note that application process for RUF questionnaire and biomarker data is separate from the application process for biospecimens. Investigators should determine if they
require biomarker and/or questionnaire data in RUFs to aid them in developing their specific aims and study design for their biospecimen request, and should allow themselves adequate time to apply and obtain these data prior to applying for PATH Study biospecimens.

2.6 RUF Data Analysis

Investigators must analyze questionnaire and biomarker RUF data using the Inter-university Consortium for Political and Social Research (ICPSR) Virtual Data Enclave (VDE). Therefore, investigators who wish to merge their newly generated biospecimen data with data from the RUF must submit their data to ICSPR. Staff at ICSPR will review the data for security issues and then upload it to the investigators’ own private secure VDE workspace. Investigators can link their data to individual participant RUF data through the Person IDs. Investigators’ biospecimen data will not become part of the PATH Study RUF and therefore, will not be accessible by other researchers.

3 Policies for Biospecimen Access

General policies for obtaining PATH Study biospecimens are listed below. Investigators are encouraged to review these policies prior to applying for biospecimens to ensure their study design, hypotheses, and planned laboratory analyses are consistent with these policies.

3.1 Eligible Applicants

Eligible applicants include independent investigators from U.S. academic, government, non-profit, or other established research institutions, including for-profit organizations. The PAR-17-458- Population Assessment of Tobacco and Health (PATH) Biospecimen Access (X01) provides additional information on eligibility requirements.

Investigators actively involved in the PATH Study can also apply for PATH Study biospecimens. However, if a PATH Study investigator is asked to review an application (either as a member of the BAC, or as an ad hoc subject matter expert), he or she must acknowledge potential conflicts of interest as soon as they become aware of them and recuse themselves as reviewers. Potential conflicts may arise in reviewing their own applications, applications of their professional collaborators, and applications for studies similar to their own.

3.2 Participant Consent and Withdrawal

The conditions for biospecimen availability based on participant informed consent and withdrawal from the PATH Study are as follows:
- Only biospecimens from participants who have signed the appropriate consent form will be released.

- Biospecimens from participants who have withdrawn from the study will not be released.

- Participants can withdraw from the PATH Study at any time and for any reason. However, if a participant withdraws after their biospecimens have been shipped to an investigator, the investigator will be notified. If the investigator has not yet analyzed the biospecimens, they will be replaced with biospecimens from a different participant with the same characteristics and the investigator will be required to destroy the biospecimens of the withdrawn participant and provide the study documentation of their destruction. However, if the investigator has already analyzed the biospecimens from the withdrawn participant, he or she will be allowed to use the results in their summary data.

The PATH Study Informed Consent form is located on the PATH Study PUF page and the PATH Study RUF page (under the “Scope of Project” section).

3.3 Biospecimen Use

Investigators must use the PATH Study biospecimens solely for the analyses described in their approved applications. Investigators may not use the biospecimens for unapproved research nor transfer the biospecimens to other investigators for unapproved research. Investigators may amend an approved protocol (e.g., study design, methods, assays, etc.) but must first request approval from PATH Study management through an addendum to their application (Section 10).

3.4 Validation Studies

PATH Study biospecimens can be used to conduct duplicate studies to confirm or repudiate the findings of an earlier non-PATH Study. Investigators should describe the goals of the validation study and justify why the earlier study needs to be confirmed or repudiated. Investigators should show that data from the two studies are comparable in terms of study design (earlier study included similar participants, time points, etc.), methods, and assays.

3.5 Collaborations

The BAC encourages collaboration between investigators, particularly under the following circumstances:

- Duplicate analyses: If two or more investigators request biospecimens to measure the same analytes on PATH Study participants with similar variables (e.g., tobacco product user groups, demographics, etc.), the BAC may encourage the investigators to collaborate with one another to conserve biospecimens. Alternatively, the BAC may request that one
investigator share his or her results with the other investigator as long as this does not affect the other investigator’s study design and aims.

- **Similar studies:** If applications with similar hypotheses or study aims are submitted by two investigators at the same time, the BAC may recommend that the individual investigators collaborate with each other. The BAC will inform each investigator that another investigator has proposed a similar study and ask them if they are willing to collaborate. The BAC will not divulge the details of the studies to the two investigators. If the investigators state they are willing to collaborate, the BAC will act as liaison and put them in contact with each other. In light of the need to conserve PATH Study biospecimens, the BAC will take an investigator’s decision of whether or not to collaborate under consideration when making recommendation for approval of a biospecimen application.

### 3.6 Pooling Biospecimens/Results from Multiple Studies

Investigators can combine PATH Study biospecimens with biospecimens collected in other studies to increase statistical power. However in these circumstances, investigators must indicate in their application their plans to pool PATH biospecimens with biospecimens from other studies, and after their application is approved, they must submit letters of commitment from collaborating investigators before the PATH Study biospecimens will be released. If an investigator does not submit the required letters of commitment, and if their hypothesis cannot be answered or their study aims cannot be met without the biospecimens from the other studies, they will not receive PATH Study biospecimens.

Alternatively, investigators can propose to pool results from their PATH Study biospecimen analyses with results already generated from other studies. There are advantages and disadvantages of pooling data in this manner. This may increase statistical power, particularly for participant subgroups. However, independent studies can differ in their measurement of key constructs, timing of biospecimen collection, and target populations. Measures of certain constructs may even differ across assessment periods within the same study. Investigators should ensure that design variables are handled appropriately to ensure that the complex design features of the PATH Study (and potentially other data sources) are reflected in estimates based on pooled data. Investigators should address this in their research strategy and statistical plan. In their applications, investigators who pool data should show that the results are comparable and that bias from differing constructs will be minimal.
3.7 **Conducting Blinded Laboratory Analyses**

Investigators will conduct all laboratory analyses on PATH Study biospecimens blinded to participant selection criteria. Investigators will be provided with information to link biospecimens to participants *after* they have completed their laboratory analyses (see Section 8.3.2).

Investigators may request unblinded biospecimens but must justify this request and describe what measures will be taken to minimize bias that might result from unblinded analyses. The procedures for requesting unblinded biospecimens are provided in Section 8.1.5.

3.8 **Biospecimen Destruction**

Upon completion of the proposed analysis of PATH Study biospecimens, investigators must destroy all residual biospecimens and provide documentation of their destruction. If instead, an investigator wishes to use the residual biospecimens for other assays or in another study, they must first obtain approval from PATH Study management through an addendum (Section 10) or new application.

3.9 **Costs for Using PATH Study Biospecimens**

If an application is approved, there will be no costs to the applicant for retrieving PATH Study biospecimens from long-term storage or packaging and shipping them to the investigators’ laboratories.

4. **Overview of Biospecimen Request/Review Process**

The process for requesting access to biospecimens includes a sequence of submission and review steps to be completed by independent investigators and the PATH Study team. An illustration of the key steps is provided in Figure 1. The review cycle timeline is described in Section 4.1. The instructions for each step in the request/review process are provided in Sections 5, 6 and 7.
4.1 Submission and Review Timeline

There will be two review cycles each year that last nine months each (Figure 2).

- **Month 1**: Investigators submit their concept statements.

- **Month 2**: The PATH Study team completes a review for completeness and checks for biospecimen availability. Investigators resubmit their concept statement, as needed, by the end of month 2.

- **Month 3**: The PATH Study team reviews concept statements for feasibility, scope, and consistency with PATH Study objectives and/or research priorities for tobacco regulatory science, and at the end of month 3, e-mails notification of decisions to investigators.

- **Months 4 and 5**: Investigators with approved concept statements prepare and submit their applications to NIH’s Grants.gov.

- **Months 6 through 9**: NIH completes administrative review of applications. The PATH Study team reviews the applications for scientific merit and impact on the PATH Study biospecimen resource, and at the end of month 9, e-mails notification of decisions to investigators.
Investigators can find the deadlines for submission, dates of review, and dates of e-mail decision notifications for PATH Study concept statements and applications in the Concept Statement and Application Submission and Review Schedule on the [PATH Study Biospecimen Access Program](#) page.

**Figure 2. Timeline for concept statement (CS) and application review cycles**

5 **Prepare to Apply**

Complete the following preparation activities prior to submitting a concept statement and application:

1. Review the [PATH Study Series](#) page to learn more about the PATH Study design, available data and biospecimens.

2. Determine whether you need access to PATH Study questionnaire or biomarker data in RUFs. Go to the [PATH Study RUF](#) page or the [PATH Study Biomarker RUF](#) page to learn how to access RUF questionnaire and biomarker data.

3. Review the Resource Access Award announcement, [PAR-17-458 - Population Assessment of Tobacco and Health (PATH Biospecimen Access (X01)](#). This form provides links to the instructions and forms on [Grants.gov](#) that you will need to complete your application.

4. If you have not already done so, complete the following registration activities that are required for submission of a grant application to Grants.gov. These are described in Section III. Eligibility Information, 1. Eligible Applicants, Required Registrations of the X01 notice. Some registrations can take 6 weeks or more to obtain.
   - The applicant investigator must have an eRA commons account.
   - The applicant institution must be issued with a Dun and Bradstreet Universal Numbering System (DUNS) number.
5. Review the Concept Statement and Application Submission and Review Schedule on the PATH Study Biospecimen Access Program page for submission deadlines, and plan accordingly.

6. Concept Statements

In the concept statement, you should provide a brief description of your project including prior relevant findings, the research hypotheses, aims, study design, and biospecimen assays. You should also list the participant criteria most important to achieving the specific aims of your project, and specify the types, numbers, and volumes of biospecimens required. The PATH Study team uses this information to: (1) match PATH Study participants to your selection criteria and check for biospecimen availability and (2) evaluate your project for feasibility, scope, and consistency with PATH Study objectives and/or research priorities for tobacco regulatory science.

6.1 Prepare and Submit a Concept Statement

Follow the instructions below to prepare and submit a concept statement:

1. Download the PATH Study Concept Statement template from PATH Study Biospecimen Access page.

2. Complete the form electronically. Refer to the Example Concept Statement for more information on how to complete each section of your concept statement.

3. Append your last name and first and middle initials, and date of submission to the file name. For example, if John Michael Smith is submitting his concept statement to the PATH Study team on September 15, 2017, the name of his file should be:

   PATH_CS_Smith_JM_2017-09-15

4. Save the file as a PDF document and send it to the PATH Study team at PATHStudyBiospecimens@westat.com.

6.2 Concept Statement Review

6.2.1 Check Biospecimen Availability

The PATH Study team will complete an administrative review of the concept statement and check for biospecimen availability as follows:
1. The PATH Study biospecimen coordinator assigned to your project will complete the following activities upon receipt of your concept statement:

   a. Assign your project a unique PATH Study Project ID #; the format of the PATH Study Project ID # is as follows:

      o **PYYYY-NNN**

         - P: PATH Study Biospecimen YYYY: Year of submission
         - NNN: Sequence number assigned to concept statement as received
         - An example of a project number is: **P-2017-002**

   b. Review the form for completeness and clarity.

      o If this is a resubmission, the biospecimen coordinator will also review your concept statement to determine if prior feedback from the PATH Study team has been addressed;

   c. Contact you by e-mail to indicate that the administrative review is complete; or to request that you revise your concept statement to address missing or inconsistent information (Section 6.3).

2. The PATH Study team will use the information in Section D (Biospecimen Availability Request Table) of your concept statement to search the PATH Study database for participants who match your selection criteria, check for biospecimen availability, and generate a Biospecimen Availability Report.

   The Biospecimen Availability Report (BAR) includes the following information:

   - PATH Study Project ID #;
   - Biospecimen Availability Report #;
   - List of participant variables provided by investigators;
   - Numbers, types, and volumes of biospecimens requested by investigators;
   - Numbers of participants available who match each individual variable and numbers of participants who match all variables. These will be listed for each participant group.

3. The biospecimen coordinator will review the report to determine if there are sufficient or insufficient numbers of participants and/or biospecimens to fulfill your request and e-mail the report to you.

4. If there are insufficient numbers of participants or biospecimens, the biospecimen coordinator will contact you as soon as possible to discuss the issues. You may be required to revise and resubmit your concept statement (Section 6.3).
6.2.2 Feasibility Review

After the biospecimen coordinator has determined that your concept statement is complete, he/she will submit it to the PATH Study BAC and PATH Study management for review. They will review concept statements for: (1) feasibility and scope; and (2) consistency with PATH Study objectives and/or research priorities for tobacco regulatory science. The PATH Study BAC will review the concept statements first and make recommendations to PATH Study management, and PATH Study management will make the final decisions. The biospecimen coordinator will notify you by email of the final decision and provide you with further instructions as follows:

- **Approved concept statements:**
  - You will be invited to submit an application.
  - You may be asked to respond to specific issues identified during the review of your concept statement. You should address these issues in your application submission.
  - The biospecimen coordinator will attach a letter from the PATH Study team to the e-mail. This letter will indicate that the biospecimens requested in your concept statement are available. **You are required to submit this letter with your application package.**

- **Denied concept statements:**
  - You will be given the reasons for the denial.
  - You may choose to resubmit the concept statement in a subsequent review cycle after addressing the reviewer’s concerns and recommendations.
  - You may submit a concept statement for review up to three times—after a 3rd denial, the concept statement will no longer be considered for PATH Study biospecimen access.

6.3 Revise and Resubmit a Concept Statement

You may need to revise and resubmit a concept statement for one or more reasons:

- **Modifications were asked for in the current cycle:** Following the administrative review of your original concept statement, the biospecimen coordinator contacted you to provide missing information or to clarify inconsistencies.

- **Revised biospecimens requested in the current cycle:** The check of biospecimen availability for your original concept statement indicated there were insufficient participants/and or biospecimens to meet your request.
- **Missed deadline for resubmitting concept statement in previous cycle:** You were unable to revise and resubmit your concept statement to meet a submission deadline.

- **Concept statement was rejected in an earlier review cycle:** Your original concept statement was denied in an earlier cycle.

Follow the instructions below to revise and resubmit your concept statement:

1. In Section A – Project Information, indicate that this is a resubmission and check all reasons that apply to your resubmission. Also provide a summary of the changes since your last submission of the concept statement. If this is a resubmission of a previously denied concept statement, be sure to indicate how you addressed the reviewers’ comments and concerns.

2. Update the file name with the date of resubmission. For example, if Joseph Michael Smith has revised his original concept statement and is resubmitting it on October 20, 2017, the name of his file should be: PATH_CS_Smith_JM_2017-10-20.

3. Save the file as a PDF and send it to the PATH Study team at PATHStudyBiospecimen@westat.com.

7 **Applications**

The PATH Study is using the NIH X01 resource access grant process to accept applications requesting PATH Study biospecimens. The PATH Study Resource Access Award announcement PAR-17-458-Population Assessment of Tobacco and Health (PATH) Biospecimen Access (X01) provides a description of the X01 application process and a link to the NIH grant application forms and instructions for preparing the application package. Application packages must be submitted through Grants.gov. They will undergo an administrative review by NIH, and then a review for scientific and technical merit by the PATH Study BAC and PATH Study management. Applications proposing meritorious and feasible studies consistent with PATH Study objectives and/or research priorities for tobacco regulatory science will be give the highest priority. Applications that address other objectives which advance the knowledge of tobacco use and/or tobacco related health outcomes will also be considered. However, the number of applications that are approved depends on the availability of biospecimens and how the request impacts the PATH Study biospecimen resource.
7.1 Prepare and Submit an Application

Prepare and submit an application as follows:

1. Go to PATH Study Resource Access Award announcement PAR-17-458-Population Assessment of Tobacco and Health (PATH) Biospecimen Access (X01) (PATH Study X01 notice) to review the requirements for preparation and submission of an X01 application, and specifically the PATH Study application through Grants.gov.

2. When you are ready to begin your application, go to the Required Application Instructions section of the X01 notice to access the application package.

3. View or download the (R) Research Instructions in the SF424 (R&R) Application Guide. It is critical that you follow these instructions except where instructed to do otherwise in PATH Study X01 notice or in a notice from the NIH Guide for Grants and Contracts.

4. Follow the Research Instructions for NIH and Other PHS Agencies – SF424(R&R) Application Packages and the PATH Study specific instructions provided in the PATH Study X01 notice to complete the following required forms:

   - SF424 (R&R) Form;
   - SF424 (R&R) Project/Performance Site Locations;
   - SF424 (R&R) Other Project Information and the following required attachments;
     - Project Summary Abstract;
     - Project Narrative;
     - Bibliography & References Cited;
     - Facilities and Other Resources;
     - Equipment;
   - SF424 (R&R) Senior/Key Person Profile and the following required attachments;
     - Biographical Sketches;
   - PHS 398 Cover Page Supplement Form;
   - PHS 398 Research Plan and the following required attachments;
     - Specific Aims (1 page);
     - Research Strategy (6 pages): See Section 7.1.1 below for additional instruction on completing the Research Strategy attachment;
     - Protection of Human Subjects;
     - Letters of Support: attach the letter from the PATH Study team which indicates that your requested biospecimens are available;
5. Complete the following **PHS 398 Research Plan** attachments only if they are relevant to your project:
   - Inclusion of Women and Minorities;
   - Vertebrate Animals;
   - Select Agent Research;
   - Multiple PD/PI Leadership Plan;
   - Appendices

6. Although the **PHS Assignment Request Form** is listed as an optional form, all PATH Study Biospecimen Access X01 applications are restricted from assignment to other than the PATH Study team for review.

7. Submit required forms and attachments to Grants.gov.

### 7.1.1 Guidelines for the Research Strategy Attachment

Use the headings in bold, and provide the information described below for the Research Strategy attachment of your application.

- **Significance:** Explain how the proposed use of biospecimens relates to PATH Study objectives, and how results will inform the scientific community, public health policy and/or tobacco regulation. Explain how the proposed project will improve scientific knowledge and technical capability for tobacco control and regulatory sciences. Describe how the study aims make use of the unique nature of the PATH Study design and biospecimens. Provide justification for requesting these specific biospecimens and explain why other sources of similar biospecimens are not appropriate.

- **Approach:** Describe how the overall research strategy and use of specific methods and analyses will accomplish the specific aims of the study. Describe how the choice of participant variables, biospecimens, assays, and statistical analyses will answer the research questions. List challenges, and potential confounders and biases that might be encountered in conducting the proposed study and what measures will be taken to minimize these issues.

- **Biospecimen Information:** List participant characteristics (variables) used to define participant groups for source of biospecimens. Describe numbers, types and volumes of requested biospecimens. Include a clear justification for number of biospecimens and volume(s) of biospecimens being requested. PATH Study biospecimens may be used to validate previous studies or used in combination with biospecimens from other studies to increase sample size and study power. However, if biospecimens are used for the latter purpose, you must show in your application that the biospecimens from the PATH Study and other studies are comparable.
- **Methodology/Assays**: List each laboratory assay planned for the biospecimens. Provide the following information for each assay:
  - Volume required (include instrument dead volume and assay volumes); multiplex assay approaches that minimize volume requirements are preferred;
  - Methodologies and instrumentation (include assay kit name if commercial kit);
  - Analyte stability and assay validation for type of biospecimen requested;
  - Assay performance (precision, specificity, accuracy, linearity of range, limits of detection);
  - Quality control (QC) plan (proportion of QC samples, estimated batch size, use of a pooled sample or individual replicates, plan for evaluating assay performance, and the source of QC samples);
  - Competency of laboratories conducting the analyses;
  - Relevant preliminary data demonstrating experience with the assay.

- **Power and Effect Size**: When appropriate, provide power calculations and anticipated size of a detectable effect for each aim.

- **Statistical Analyses**: Provide a detailed statistical analysis plan including the following: enumeration of all exposure and outcome variables (primary and secondary) and covariates; statistical models and assumptions; plans for evaluating assumptions required by the models; and other statistical issues germane to the proposed research such as measurement error, multiple comparison testing, bias, interactions, and data adjustments. Individuals conducting data analyses should include their biosketches with the application, even if they are not senior/key personnel on the project.

### 7.2 Application Review

Your PATH Study application will undergo an administrative review and a scientific and technical review. It will also be reviewed for the impact the biospecimen request will have on the PATH Study biospecimen resource. The goals of the review process are to ensure fair, equitable access to PATH Study biospecimens in the short-term while balancing the need to preserve biospecimens for future use in the long-term.

#### 7.2.1 Administrative Review

After submission, your application will be transmitted electronically to NIH. NIH will conduct an administrative review of your application and notify you of any issues that need to be addressed. Once all issues are addressed and your application is considered complete, NIH will submit your application to the PATH Study team.
The biospecimen coordinator assigned to your project will complete the following activities upon receipt of your application:

1. Review the application for completeness and clarity;
2. Review the application for consistency with your approved concept statement for participant selection criteria and requested biospecimens.
   - Any changes made in participant selection criteria and/or in the types, numbers, and volumes of biospecimens that were previously approved in the concept statement will require a recheck of biospecimen availability. Any biospecimens insufficiencies identified by the recheck could significantly delay review of your application.
3. Contact you by e-mail to indicate that the PATH Study administrative review is complete; or request that you revise your application to address missing or inconsistent information.
   - If you are required to revise your application, the biospecimen coordinator will provide you with specific instructions on how to revise and resubmit your application. You may be required to address simple administrative issues or changes that you made in participant selection criteria and/or request for biospecimens. The biospecimen coordinator will also give you a deadline for the resubmission. If you miss this deadline, your application may not be reviewed in the current cycle but be placed in the queue for the next cycle.

### 7.2.2 Scientific Review

After the biospecimen coordinator has determined that your application is complete, he/she will submit it to the PATH Study BAC and PATH Study management for review. The BAC will evaluate your application for scientific and technical merit on the individual review criteria listed below. The BAC also will evaluate the impact your application will have on the PATH Study biospecimen resource (e.g., determine whether approving an application will deplete biospecimen resources for a particular subgroup of PATH Study participants). Based on the scientific review, the BAC will make an approval recommendation to PATH Study management. PATH Study management will make the final decisions. The biospecimen coordinator will notify you of the final decision and provide information on next steps as follows:

- **Approved applications:**
  - You will be given instructions on next steps to initiate your project and a list of post-approval documents to submit. Your PATH Study biospecimens will be shipped only after these tasks are completed.
Denied applications:

- You may choose to resubmit the application or apply to repeal the denial (see Section 9).

### 7.2.2.1 Scientific Review Criteria

Reviewers will consider each of the individual review criteria below in the evaluation of each application. These review criteria follow NIH standard criteria and criteria specific to the PATH Study Biospecimen Access X01.

**Individual (Scored) Review Criteria**

**Significance:** Does the project address an important problem or a critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

- Does the application describe how successful completion of aims will contribute to scientific knowledge and improvements in technical capability for tobacco control and regulatory science?
- Can the study aims be accomplished using PATH Study biospecimens and data?
- Do the specific aims address PATH Study objectives?
- Have the investigators provided adequate justification for use of PATH Study biospecimens and successfully explained why other sources or similar biospecimens are not adequate?
- Does the proposed research make use of the questionnaire and biomarker data associated with the biospecimens to help answer the research question?

**Investigator(s):** Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or New Investigators, or in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

**Innovation:** Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

**Approach:** Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential
problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or humans?

- Are the variables selected to define participant groups appropriate for fulfilling the specific aims of the study?
- Are the types, numbers and volume of samples justified?
- Have the proposed assays been validated for use with the specific types of biospecimens requested? Have sufficient preliminary data been presented to demonstrate accuracy and robustness of the proposed assays? Has the applicant provided assay validation data? If multiple assays are available for a proposed analyte, has the applicant justified their choice for using a particular assay? Did the investigator describe the laboratory quality control plan and if so, is it adequate?
- Did the applicants provide effect sizes and use power calculations to determine the sample sizes needed to detect significant effects for each aim? Did they state the power levels they wished to achieve with the proposed sample sizes?
- Does the statistical analysis plan adequately describe the data that will be analyzed and the statistical methods that will be used? Does the plan address statistical issues germane to the research such as measurement error, multiple comparison testing, bias, interactions, and data adjustments? Are individuals with sufficient expertise and experience proposed to conduct the data analyses?
- If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Environment: Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

Additional Criteria

Reviewers will evaluate additional criteria only if they are relevant to the application under review. These additional criteria include: protections for human subjects; inclusion of women, minorities and children; vertebrate animals; and biohazards.
8  Project Initiation

After your application is approved, the PATH Study team will contact you to initiate project activities including, post-approval activities, biospecimen shipment and analysis, and reporting. Project initiation activities are outlined in Figure 3.

Figure 3. Project initiation activities

- Submit Post-Approval Documents
- Execute Material Transfer
- Approve Participant Selection
- (Optional) Request Approval Letters and Unblinded
- Ship Biospecimens
- Conduct Laboratory Analysis
- Submit Annual Reports
- Destroy Residual Biospecimens and Submit Documentation of
- Submit Final Report
8.1 Post Approval Activities

Once your application is approved, you have 12 months from the date of approval to conduct the required and optional post-approval activities described in this section. These activities must be completed before PATH Study biospecimens are released for shipment to the laboratories designated in your application.

8.1.1 Submit Post-Approval Documents

As soon as possible after your application is approved, submit the following required documents to the PATH Study team:

- **Proof of Funding** – Official documentation of proof of funding to ensure you can cover the costs of the project and/or the biospecimen analyses. Alternatively, you can submit a letter of commitment from the laboratory or collaborator who is conducting your laboratory analyses (see third bullet).

- **IRB Documents** – If you are required by your institution to have your project undergo full IRB review, then you must submit the final IRB protocol and official IRB approval letter. If you are seeking exemption from IRB review, you must submit the official letter from your IRB granting you IRB exemption.

- **Letters of commitment from other investigators** – Submit letters of commitment from investigators that are providing important resources to your project especially if these resources are critical to your project. These could include an investigator who is giving you biospecimens from their study to use in combination with the PATH Study biospecimens (e.g., to increase study power) or an investigator giving you a valuable reagent they developed in their laboratory (e.g., antibody). As you obtain these documents, send them to the PATH Study team at PATHStudyBiospecimens@westat.com.

The PATH Study team will review the documents to ensure that the uses of the PATH Study biospecimens outlined in the documents are consistent with their uses as indicated in your approved application.

The PATH Study team also will track submission of your documents. If your application remains inactive for more than 12 months after its approval date due to lack of funding, inability to obtain IRB approval, or other issues, the PATH Study team will contact you to discuss the reasons for the delay and present them to the BAC for review. The BAC will recommend for or against extending your project initiation period and PATH Study management will make the final decision. If an extension is not granted, you must submit a new application to reactivate your project.
8.1.2 Execute Material Transfer Agreement (MTA)

After you have submitted the post-approval documents, the PATH Study Team will contact you to initiate execution of the PATH Study MTA and act as liaison between you and the NIDA technology transfer specialist.

The PATH Study MTA is a binding legal agreement between you and NIDA covering the shipment, use of, and disposition of the PATH Study biospecimens you receive under the approved application. Execution of this agreement is required before biospecimens will be shipped.

If at any time during this agreement, you change your affiliation from what is listed on the MTA, you must notify the PATH Study team.

Following execution of the MTA, the PATH Study team will contact you via email to obtain the address to which to ship your specimens.

8.1.3 Approve Participant Selection

The PATH Study team will make a preliminary selection of participants to fulfill your request. You will be asked to review and approve the participant selection as follows:

1. You will be notified to download a report from Westat’s secure FTP website. The report will provide:
   - Variable labels and their value descriptions for the specifications provided by the investigator to select the participants.
   - Participant level data will be listed for each selection variable (e.g. male, Caucasian, exclusive cigarette user, cardiovascular disease, etc.).

2. Review the selection variables and data in the report to ensure the participants listed meet your study needs.

3. Notify the PATH Study team (PATHStudyBiospecimens@westat.com) that you approve the participants listed in the report or have issues with the variables used to select them. The PATH Study team will work with you to make a final selection.

4. Once you approve the participant selection, the PATH Study team will reserve biospecimens of the appropriate matrix and volume from these participants for 12 months following the date of application approval.
8.1.4 Request Approval Letters from PATH Study

You can request letters of approval from the PATH Study confirming that you have been approved to receive PATH Study biospecimens. These might be needed if you are applying for grants or other sources of funding for your project. They also might be requested from other investigators who are considering committing valuable resources to your project.

All requests for approval letters should be made directly to the PATH Study team (PATHStudyBiospecimens@westat.com). The letters will be drafted and addressed to the persons, affiliations, and addresses indicated in your request. The letters will be addressed from PATH Study management and state that you have been approved to receive PATH Study biospecimens.

8.1.5 Request Unblinded Biospecimens

As indicated in Section 3.7, you must conduct all laboratory analyses on PATH Study biospecimens blinded to selection criteria. However, if this requirement will impact your analyses (e.g., sensitivity, linearity of the assay), you may submit a request to conduct unblinded or partially unblinded analyses. The request must include a justification and describe the measures that will be taken to minimize bias that might result from unblinded analyses. Submit this request to the PATH Study team at PATHStudyBiospecimens@westat.com.

The PATH Study team will submit the request for unblinded analyses to the BAC. If the BAC approves your request, you will be given access to a file linking the aliquot IDs on your biospecimen vials with individual participants via their Person ID number. The Person ID is used to identify participants in the RUF data files (Section 2) and in the participant selection file (Section 8.1.3).

8.2 Shipping Biospecimens

8.2.1 Coordinate Shipping Logistics

Once all post-approval activities are completed, the PATH Study team will contact you by email to arrange shipment of the biospecimens. The email will include the: (1) name and shipping address of the laboratory; (2) name and contact information of the person at the laboratory responsible for the shipment; (3) shipment date; and (4) a list of analytes that will be measured on the biospecimens. Once this information is obtained, the PATH Study team will work with the biorepository to prepare the shipment.
8.2.2 Ship Biospecimens

On the day of the shipment, a Biospecimen Manifest will be e-mailed to you. The manifest will list the following:

- Aliquot ID – the barcoded ID on the specimen vial;
- Diagnostic test – a code indicating the intended assay for the shipped specimen;
- Aliquot volume – quantity and units specifying the volume of material in the vial;
- Other observations – flexible text field, use to indicate biospecimen matrix or other;
- Box – the barcoded ID on the plate;
- Row – row position on the plate;
- Column – column position on the plate;
- Shipment number – Fisher shipment identifier;
- Tracking number – FedEx tracking number for the shipment.

All biospecimens will be shipped by overnight express on dry ice. Upon receipt, the contact person at the laboratory will be required to confirm receipt of samples and provide documentation. If any issues are identified with the aliquots, the PATH Study team will work with you, and the laboratory and biorepository to resolve them.

8.3 Biospecimen Analyses

8.3.1 Timeline for Completing Biospecimen Analyses

You are required to complete the biospecimens analyses within two years of the date of biospecimen receipt. The PATH Study team will track your progress by monitoring annual and final progress reports (Section 8.4).

If you do not complete your analyses within two years of the biospecimen receipt date, the PATH Study team will contact you to discuss the reasons for the delay and present them to the BAC and PATH Study management for review. If an extension is not granted, you will be required to ship the biospecimens back to the biorepository.

8.3.2 Unblinding Biospecimen Results

After you have completed the laboratory analysis of your biospecimens, you should contact the PATH Study team to request unblinding of your biospecimens. The PATH Study team will instruct
you to download a file from Westat’s secure FTP site. This file will link the IDs on your biospecimen vials with individual participants via their Person ID number.

### 8.3.3 Destruction of Residual Biospecimens

You must notify the PATH Study team when all of your approved biospecimen analyses are complete. You will then be instructed to destroy all residual biospecimens and to provide documentation of their destruction. Alternatively, you can request to use the residual biospecimens in a follow-up study by submitting an addendum to your application (see Section 10).

### 8.4 Progress Reports

You must inform the PATH Study team of your progress, first in completing project initiation activities and subsequently, in analyzing biospecimens and disseminating results, by submitting annual and final progress reports to the PATH Study team at PATHStudyBiospecimens@westat.com.

#### 8.4.1 Annual Progress Reports

Your first annual report is due one year after the date your application is approved. If you are still conducting post-approval activities and have not yet received your biospecimens, include the following information in your report:

- Timeline for completing post-approval activities;
  - Submit proof of funding;
  - Submit IRB documents (protocol, approval, exemption);
  - Submit Letters of commitment from other investigators providing biospecimen resources;
  - Execute Material Transfer Agreement;
  - Approve Participant Selection report.

If you have completed your post-approval activities and have received your biospecimens, include the following information in your report:

- Timeline for analyzing biospecimens if not yet begun;
- Progress on biospecimen analyses;
- Progress on data analysis;
- Status of residual biospecimens (e.g., plans to destroy, already destroyed and documentation submitted, addendum submitted to request use in a follow-up study);
- Plans for disseminating results.

If you do not submit an annual progress report within 30 business days after the deadline, and have not yet received any biospecimens, your application will be withdrawn and you will not receive the PATH Study biospecimens. You will be required to submit a new application during the next review cycle. If you have already received your biospecimens and do not submit an annual progress report within 30 days after the deadline, any future PATH Study biospecimen applications you submit may not be considered.

### 8.4.2 Final Progress Report

Your final report is due within six months after you complete your biospecimen analyses. Provide the following information in the report:

- Status of residual biospecimens (e.g., plans to destroy, already destroyed and documentation submitted, addendum submitted to request use in a follow-up study);
- Plans for disseminating results;
- Submission of manuscript citations;
- Future plans for additional studies with PATH Study biospecimens.

If you do not submit a final progress report, any future PATH Study biospecimen applications you submit may not be considered.

### 9 Denied Applications

Your applications may be denied for a number of reasons such as:

- Study design or other study component has significant weaknesses;
- Application is poorly written;
- Application is not consistent with PATH Study research objectives or tobacco regulatory sciences and it does not expand the knowledge of tobacco use and/or tobacco related health outcomes;
- PATH Study biospecimens are not appropriate to address the proposed study aims and hypotheses;
- Numbers and/or volumes of requested biospecimens would place a significant burden on the PATH Study biospecimen collection.
You may choose to revise and resubmit the application (9.1) or to appeal the denial (9.2).

9.1 Revise and Resubmit a Denied Application

If you plan to revise and resubmit an application, you should contact the biospecimen coordinator at PATHStudyBiospecimens@westat.com for specific instructions. You can submit an application for review up to three times—after a 3rd rejection, the application will no longer be considered for PATH Study biospecimen access.

9.2 Appeal a Denied Application

If you choose to appeal a denied application, you must submit a formal appeal letter to PATH Study team at: PATHStudyBiospecimens@westat.com within 30 days following the date of your application rejection notification. The appeal letter must describe specific issues with the review. Appeals based solely on differences of scientific opinions will not be accepted. PATH Study management will review the appeal letter and decide whether further review of the application by other scientists is needed. You will be notified of the final decision by e-mail. The outcome of an appeal is final and the application cannot be appealed again.

10 Addendums

Addendums can be submitted to the PATH Study team at PATHStudyBiospecimens@westat.com any time after your application is approved. You can use an addendum to request changes in the scope, methods, and design of your study. You also can use an addendum to request additional biospecimens or to request the use of residual biospecimens for a related pilot study or small-scale follow-up analyses.

In the addendum, you will be asked why you are requesting changes to your project and to explain the differences between the original application and new request. You must indicate whether the changes will require new funding and/or new IRB or other approvals.

10.1 Request Additional Biospecimens

If you are submitting an addendum to request additional biospecimens, the PATH Study team will use the information you provide in the addendum (i.e., participant variables and numbers, types, and volumes of biospecimens) to determine biospecimen availability and generate a Biospecimen Availability Report. If the team finds there are insufficient numbers of biospecimens available that match your addendum request, they will notify you and work with you to resolve the insufficiencies.
10.2 Request Use of Residual Biospecimens

Instead of destroying residual biospecimens, you may request to maintain them in your laboratory and use them for future follow-up studies by submitting an addendum. The addendum should include a description of future plans and timelines for use of residual biospecimens. If your addendum is approved, you may be required to comply with specific conditions under which the residual biospecimens can be used or maintained.

10.3 Addendum Review

Addendums will be reviewed by the PATH Study team upon submission for completeness and clarity, and will be returned to you if they do not meet these requirements. Once an addendum is deemed complete, it will be reviewed by the BAC and PATH Study management. The addendum may be approved or denied. Alternatively, if the scope and size of an addendum is considerable, you may be asked to submit a new biospecimen concept statement and/or application. You will receive an email notification of the decision within two months of submitting your addendum.

11 Share Biospecimen Results

You are required to share the data generated from PATH Study biospecimens to the greatest extent possible, consistent with the NIH Data Sharing Policy (https://grants.nih.gov/grants/policy/data_sharing/) and the policies set forth by the project funding agency(ies). You can share data by: (1) depositing the data in a public data repository; or (2) publishing it in peer-reviewed journals. Such data sharing would begin after you are given an appropriate time to publish and/or obtain intellectual rights to the data. If you wish to share data using option 1 above, the website below provides a list of NIH data repositories where you can deposit their data.


12 PATH Study Acknowledgement

When you publish the results of your PATH Study biospecimen research, you should acknowledge the PATH Study by using the following language:

These analyses were conducted using materials whose collection was funded by the United States Department of Health and Human Services, National Institutes of Health, National Institute on Drug Abuse, and United States Department of Health and Human Services. Food and Drug
13 Cite Publications

When you publish data generated from analysis of the PATH Study biospecimens, you must adhere to NIH Public Access Policy (2008) (https://publicaccess.nih.gov/policy.htm) which requires you to submit or have submitted for you, all manuscripts accepted for publication, on the National Library of Medicine’s PubMed Central. You must also adhere to any policies set forth by the project funding agency(ies). In addition, we recommend that you send the final manuscript citation to NAHDAP at https://www.icpsr.umich.edu/icpsrweb/ICPSR/citations/submit.jsp for inclusion in the PATH Study bibliography. You can do this on the PATH Study Series page. Under “For Researchers,” select “How to submit your citations to the ICPSR Bibliography” and complete the form.