Project Viva Policies

Grant Applications, Analyses, Ancillary Studies and Publications/Authorship
3/11/24

The purpose of this document is to have everyone involved with Project Viva understand the basic policies for grants, ancillary studies, analyses, and publications. Project Viva is a complex web of interrelated funded projects and unfunded analyses. With these policies, we aim to avoid misunderstandings and to retain a collegial relationship among all investigators and staff in our efforts to conduct high quality science as efficiently as possible. We will update these policies yearly, or as necessary. We welcome comments on these policies from all collaborators and staff.

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I. Decision-Making Authority

Collaboration and participation are the underlying principles. The Viva PIs and major Co-Investigators make up the decision-making group (DMG) for approving grant applications, analysis proposals, and publications. In virtually all decisions, we envision a consensus among the PI/Co-PI/Co-Is. Should an impasse exist, the Viva PIs have final authority.

A Viva Co-I is anyone listed as a Co-I on the NIH grants that support the majority of Project Viva operations, or the PI of one of the other grants that support Viva operations or analyses. In addition to being listed as a PI or Co-I, one must also be actively involved with the Co-I meetings and operations. The DMG may also, at its discretion, appoint other collaborators to the group if they are substantially involved. The list of currently funded grants (as of January 2024) is as follows:

1. Prenatal environmental determinants of health in young adulthood: a lifecourse approach (Oken and Hivert, MPIs)
   NICHD R01 HD 034568
2. Common and distinct early environmental influences on cardiometabolic and respiratory health: Mechanisms and methods (Oken and Kleinman, MPIs)
   NIH OD UH3 OD023286
3. A lifecourse approach to women's cardiometabolic and bone health: from fertility to perimenopause (Oken and Chavarro, MPIs)
   NICHD R01HD096032
4. Long-term health consequences of birth by cesarian section (Chavarro and Oken, MPIs)
   NICHD R01 HD 093761
5. Environmental Chemicals, Adiposity, and Bone Accrual across Adolescence (Fleisch PI; Oken, Site PI)
   NIEHS R01 ES030101
6. Physiologic and social stressors and health during the menopausal transition (Oken and Chavarro, Project MPIs; Joffe Program PI)
   NIA 1U54AG062322-01A1
7. Maintain and Enrich Resource Infrastructure for Project Viva: a pre-birth cohort with follow up into adolescence (Oken, PI; Switkowski, Project Lead)
   NIEHS R24ES030894-01
8. Long-term prospective associations of PFAS with musculoskeletal and cardiovascular health among older adults (Oken, PI)
   NIEHS R01ES024765
9. Epigenetics, Air Pollution, and Childhood Mental Health (Brunst PI; Hivert, Site PI)
   NIEHS R01ES031054

10. Prenatal and Postnatal Exposure to Environmental Mixtures: Neurodevelopment and DNA Methylation Biomarkers (Cardenas, PI; Oken, Site PI)
    NIEHS R01ES031259
11. Per- and Polyflouroalkyl Substances Mixtures and Maternal Cardiovascular Disease Risk Across the Reproductive Life Course (James-Todd and Zota, MPIs; Oken, Site PI)
    NIEHS R01ES031065
12. Toxic substances in the environment (Oken, Site PI; Cardenas and Smith, MPIs)
    NIEHS 2P42ES004705-34
13. Developmental origins of optimal cardiovascular health across childhood and adolescence (Aris, PI)
    AHA 23CDA1050962
14. Neighborhood Vulnerability and Menopause and Cardiovascular Health in Midlife Women in Project Viva (Aris, PI)
    NIH 5U54AG062322-04
15. From Pregnancy to Mid-life: Metal Mixtures and Health Behaviors Shaping Maternal Cardiometabolic Health Over 20 Years (Zhang, PI)
    AHA 24CDA1257852
16. Diversity Supplement for U54: Climate-related factors and health during the menopausal transition (Soria-Contreras, PI)
    NIA 3U54AG062322-04S2
17. Early life exposure to metal mixtures: impacts on asthma and lung development (Thilakaratne, PI)
    NIEHS 1F31ES034639-01A1

We will invite other collaborators to meetings at which their input will be especially helpful, but they are welcome at all meetings. In addition, we will always include in decision-making a collaborator whose unique contribution to the study is under discussion. Examples of these contributions include a set of questions on a questionnaire or a particular procedure. In practice, the PI/Co-Is who are present at a particular meeting comprise the decision-making group.

II. Grant Applications

Grant funds are the lifeblood of Viva, and they are the mechanism to explore novel scientific ideas. Therefore, we welcome grant applications from investigators both previously involved and newly collaborating with Viva. We support junior investigators to become more independent by looking for opportunities for them to become PIs on Viva-related grants.

Investigators wanting to write grants that involve Viva Data and/or Viva-related activities must first communicate with the Project Viva PIs and the Program Manager. Prior to submitting any grant proposing to use Project Viva data, the proposing investigator must present the grant aims for scientific review and approval at a Co-Investigator meeting. Additionally, for any grant that would require staff time or lead to additional participant burden, the investigator should also plan to attend a Data/Operations meeting to discuss the administrative and budgetary implications. This discussion will help to ensure that the proposal will not interfere with or duplicate ongoing activities and will provide information to assist with preparation of a subcontract. The investigator should contact the Program Manager to determine whether a Data/Ops presentation is warranted, and to schedule it. Please see below under Viva Ancillary Studies → Other Ancillary Studies → Process for Proposing a Project Viva Ancillary Project for more information. All grants must be self-sufficient, that is, pay for all proposed activities including but not limited to: the cost of pulling stored biospecimens, preparing and shipping samples, any assays, incentives for participants, and effort of the Project Viva staff.

As a general rule we anticipate that any grant proposal involving Project Viva data will include funding for Project Viva via a prime award based at Harvard Pilgrim Health Care (HPHC), or via a subcontract to HPHC, to support Project Viva investigator and staff effort as appropriate to the project. The proposer may be the PI or MPI on the proposal, depending on such circumstances as:

a) administrative issues, such as to what institution the proposer is appointed;
b) seniority of the proposer; and,
c) overlap with interests of previously involved investigators.

If grant aims previously approved at a Co-Investigator meeting are subsequently funded, the investigator must plan to re-present their analysis proposal at a Co-I meeting prior to receiving an analytic dataset, unless they explicitly receive approval from a Project Viva PI to move forward without doing so or to present the analysis proposal in a different setting. If the funded grant requires a data/sample sharing agreement, the PI outside of HPHC should review the agreement template (provided to them during the pre-award process) with their grants and/or contract staff as soon as possible after being informed about the grant being awarded. The agreement execution process can begin as soon as funding contracts are executed between the two institutions.

III. Viva Ancillary Studies

A. Overview

As time progresses, Viva's data set grows, and scientific knowledge evolves. We now have over 25 years of data that lend themselves to studying associations Project Viva had not previously considered. Project Viva can thus serve as a great platform to conduct ancillary studies. These ancillary studies will further scientific knowledge and enhance the depth of information gained from Project Viva.

We welcome ancillary study proposals from outside investigators, including students, fellows, and faculty. If the proposing investigator is a trainee (student or post-doc) then they should ensure that their primary supervisor is aware of the request and willing to serve as a mentor on the proposed project, which includes ensuring that the trainee follows best practices for analysis and reporting of scientific results.

As noted above, Project Viva would not exist without ongoing, external funding. We do welcome proposals to analyze existing data that are unfunded, especially those led by students and trainees. However, funded projects will take priority.

B. Ancillary Study Definitions

i. Data Repository Ancillary Studies

The goal of the Viva Data Repository is to streamline the process of data analysis for outside investigators while protecting the privacy and confidentiality of our participants. An ancillary study that falls under the Project Viva Data Repository involves the use of pre-existing, de-identified Project Viva data on all or part of the cohort. These studies are generally led by an investigator, herein referred to as the proposing investigator, with no affiliation to HPHC. If the proposing investigator is a Co-I on a Project Viva non-repository protocol, it must be confirmed they do not have access to study PHI before they can propose a repository analysis. If a study meets all criteria for a data repository ancillary study, no HPHC IRB review is required. A study that involves a topic not covered by the consent form does not qualify as a data repository ancillary study, and requires a separate application to the HPHC IRB. See below (III.B.i.d) for further information regarding epigenetic analyses which are included as Data Repository Ancillary Studies. A study that involves genetic analyses does not fall under this general Viva Data Repository protocol but may qualify as a Project Viva Genetic Repository ancillary study; please refer to the separate Viva Genetic Data Policy documentation.

a. Analyses of Viva data only

If an ancillary study involves analysis of data from Project Viva only, the lead investigator should follow procedures outlined in III.C. *Process for Proposing a Project Viva Ancillary Study*

b. Studies including analysis of data from Viva as well as other datasets or cohorts.

In some cases, investigators may request Project Viva data to serve as an additional data resource or replication dataset for an analysis. If the goal of including Viva data is to increase the sample size or conduct parallel or combined analyses within several data sets or cohorts simultaneously, and Viva collaborators will help refine the analysis plan, then the lead investigator should follow procedures outlined in III.C. *Process for Proposing a Project Viva Ancillary Study.*

If the goal of including Viva data is external replication of an analysis approved for and already conducted within another dataset, then the lead investigator should reach out to the Viva PI(s) who will determine the most appropriate place for review, which may be Co-Investigator meeting or another content-focused investigator meeting such as the 'omics meeting, mixtures meeting, etc.

c. Meta-analyses

Over the years, Project Viva has contributed data to various meta-analyses, led by research consortia or by individual investigators or groups. We continue to welcome such proposals.

For such meta-analyses, the lead investigator may request pre-existing, de-identified Project Viva data on all or part of the cohort. These data may be requested as tabulated results, or in some cases, as individual-level data. All such analyses should have been posted publicly on a protocol repository such as Prospero (https://www.crd.york.ac.uk/prospero/) or an existing consortium (e.g. PACE for epigenetics). The proposing investigator will communicate their request and will provide the analysis plan, link to registry posting, and IRB/ethics approval from their own institution (or determination of exemption from such review) to Project Viva's Program Manager. The Project Viva Program Manager will provide a copy of the data request and analysis plan to Project Viva's MPI, Dr. Oken and/or Dr. Hivert, and to other Viva Co-Investigators as appropriate, depending on the topic of the proposed analysis. These investigators will review the proposal for scientific merit and will determine whether Project Viva has the required data elements and resources necessary to contribute to the

analysis. Recognizing that a meta-analytic protocol needs to be common across all sites and cannot be modified for each cohort, we do not require presentation and review at a Co-Investigator meeting but will share the title of each approved meta-analysis at the subsequent Co-I meeting so that all Viva Co-I's are aware of the ongoing project.

If the Viva PI and other investigators approve Project Viva's contribution to the proposed analysis, the Program Manager will communicate a request for data and deadlines to the Project Viva Data Manager and/or Lead Research Analyst. The Project Viva Program Manager will be responsible for tracking all projects and required documentation, and the Lead Research Analyst and/or Data Manager will be responsible for generating the requested dataset or summary statistics. Project Viva's Program Manager will request the necessary documentation and attestation, as outlined in Section III.C below, from the lead investigator before the requested dataset is provided. One or more Project Viva investigators may participate as coauthors in publications resulting from such a request, depending on the topic area and assuming that they meet standard requirements for authorship.

If the proposed project is a meta-analysis utilizing genetic data, please refer to our Viva Genetic Data Policy documentation at www.ProjectViva.org.

d. Epigenetic Analyses

Epigenetic analyses that do not include genetics are covered under the Viva Data Repository. The Project Viva Data Repository includes epigenetic data from a subset of the Project Viva cohort who:

a. Provided blood or nasal swab samples at one or more in-person visits
b. Consented to use of their biospecimen samples for epigenetic analysis. Beginning with the Early Teen visit, we allowed participants to provide consent specifically for epigenetic analysis of their bio samples—whether obtained in the past, currently, or in the future—separately from consent for genetic and other analyses. We also include data from participants who did not complete an Early Teen visit but provided consent for genetic analysis of their bio samples at previous visits.

Thus far, Project Viva has performed epigenomic assays and generated epigenomic data from cord blood, early childhood blood, mid-childhood blood, early teen blood, and early teen nasal cell samples. Investigators wishing to perform epigenetic analyses should follow the processes outlined in III.C. Process for Proposing a Project Viva Ancillary Study. If the proposed analyses are part of a planned meta-analysis, we do not require

presentation and review at a Co-Investigator meeting. Investigators should follow similar procedures as outlined above in section III.B.i.c (Meta-analyses).

ii. Other Ancillary Studies

Other types of ancillary studies, such as research plans that request Protected Health Information (PHI) or direct access to medical records; grant proposals to fund data collection; or requests for biospecimen samples to analyze, do not fall under the data repository but are also welcomed and encouraged. Please see sections below for guidance on non-repository ancillary studies.

C. Process for Proposing a Project Viva Ancillary Study

Investigators can request approval for an ancillary study by presenting an analysis plan at a monthly Co-I meeting (see Section IV.A below). Following the presentation, the DMG will: 1) approve the analysis plan or 2) recommend that the proposing investigator revise the plan and resubmit for PI review, 3) recommend that the proposing investigator revise and present again at a future Co-I meeting or 4) decline Project Viva participation in the proposed project.

In addition to receiving scientific approval of the analysis plan, any investigator proposing an ancillary study (including Data Repository ancillary studies) must provide the following to the Project Viva Program Manager before requesting a dataset:

1. Documentation of IRB review from the investigator's home institution. The proposing investigator should contact their IRB to determine IRB requirements. (Contacts for local institutions can be found at: https://connects.catalyst.harvard.edu/profiles/search/people.) The proposing investigator should provide the Project Manager with either: 1) documentation of IRB approval, or 2) documentation or communication from their home IRB stating that the proposed project has been determined to be Not Human Subjects Research or otherwise exempt from IRB review.

2. A current CITI certificate (certificates expire after 3 years). CITI certification can be completed at www.citiprogram.org.]

We welcome analyses led by investigators from other countries and recognize that training and approval requirements differ from those in the US. We require that investigators follow and provide us with documentation of adherence to all policies required by their home institution, which may or may not require regular training in human subjects research.

3. A statement acknowledging that the proposing investigator has read and agrees to abide by Project Viva's data use and sharing policies.

4. A copy of the investigator's CV.

In addition, investigators proposing a project that does not fall under the Viva Data Repository and/or that may impact Viva operations, participants, or biospecimen, may be asked to attend a Project Viva Data/Operations or other appropriate meeting identified by the Viva PIs/PM to present an operational proposal (*Note: this proposal will be focused on operational considerations, and is different from the more scientific analysis plan that the proposing investigator will present at a Co-I meeting). The proposing investigator should contact the Viva Program Manager to arrange this. The process is as follows:

1. The investigator will present a proposal, which should include:
    - Study aims
    - Description of proposed research activities, specifically focused on any new data collection (e.g. collection of new data elements or biospecimens, or analysis of existing biospecimens).
    - Identification of study sample and inclusion/exclusion criteria, if applicable
    - Information about any requested bio samples, including visit, N, and volume (see policies for biospecimen sample use in Appendix V)
    - Proposed IRB reliance structure to align with single IRB requirements
    - Proposed timeline
    - Confirmation of allowable payment arrangements from the funder, e.g., does the funder allow a subcontract? All ancillary studies must be self-sustained (see budgeting guidelines in Appendix IV).

2. The Project Viva PI and Co-PI, Program, Project and Data Managers, Lead Research Analyst, and other key staff will evaluate the proposal based on the following factors:
    - Fit with Project Viva's overall goals
    - Operational (staff) burden
    - Participant burden, including how the proposed project may affect long-term participation
    - Availability of biospecimen samples
    - Amount of funding available from the proposer. Please see Appendix IV for budgeting guidelines to help investigators to determine if the available funding will be sufficient to cover staff effort and other requirements.
    - Whether the proposed project takes advantage of Project Viva's unique strengths.

3. If the proposal is approved by the Viva team from an operational perspective, the proposing investigator also needs to present an analysis plan at the Viva Co-Investigator meeting for scientific review and approval.

4. If Project Viva approves the project, the proposing investigator will also be responsible for providing information on an ongoing basis. Documents will include:
    - Research protocol for the IRB
    - Up-to-date list of all outside staff involved in handling samples/viewing data and confirming they are listed on their home institution's IRB
    - CITI training certificates and CVs as requested
    - IRB Documentation
        - Cede Review reliance agreement. Investigators considering requesting to cede review to or from HPHCI should first discuss this with the Project Viva Program Manager.
        - If the proposing investigator's IRB reaches a non-human subjects determination, the HPHCI IRB will still require submission of a research protocol. The proposing investigator will be responsible for completing the required forms for the HPHCI IRB, with assistance from the Project Viva staff.
    - Updates on study progress when requested and copies of all resulting publications/presentations (e.g. for yearly Continuing Review).

Ancillary studies that do not fall under the data repository will generally also require a data transfer agreement. If the study involves analysis of Project Viva biospecimen samples, a data transfer agreement with an appendix regarding sharing samples will also be required. The investigator should allow 2-4 months for completion of all of these requirements, although this is also dependent on the requirements of the investigator's institution. If the study involves biospecimen samples, we require the proposing investigator to read the data transfer agreement template ahead of grant submission, and to review it with their grants and/or contracts staff to ensure there will be no issues in executing the agreement should the award be funded.

After all the above requirements are met (and, in the case of a funded project, funding is obtained), the investigator may request a dataset from the Lead Research Analyst (the Program Manager will be informed of this request). All data generated from new assays must be sent directly from the assay lab to the Project Viva Program Manager and/or Lead Research Analyst, who will review and prepare the data to be included in the data set requested by the investigator. Assay labs must not send newly generated data directly to investigators outside of HPHCI, regardless of assay funding source.

Upon requesting and receiving Project Viva data (datasets or summary results), the proposing author agrees to follow all Project Viva policies as outlined in this document. They may use the data only for

purpose originally requested (except if written agreement stating otherwise). Approval must be granted by Viva's DMG and the HPHC IRB, as required, for additional use of the data. Additional investigators also permanently based at the lead investigator's research site may collaborate with them on their project and have access to their de-identified data set, however, the lead investigator is first responsible for ensuring they have attested to these policies, and that they are approved on any relevant IRB protocol and have completed required institutional human subjects research training.

This policy provides general guidance; each proposal will be considered individually by Project Viva's operational leadership; specific requirements may differ from what is listed above. Ancillary studies will be guided by the Viva Co-Investigator review, manuscript review and authorship requirements outlined in these policies. Viva Co-I and departmental review are required to protect our participants and the quality and integrity of Project Viva data.

D. Data Repository & Security

Project Viva data collection began in 1999 and continues to date. All data have been obtained by written informed consent or through a waiver granted by HPHC's IRB. Project Viva data has been collected from in-person, remote, and mailed visits, currently approved under the following two protocols:

- Child Cohort Data – IRBNET #235301: *Project Viva: A longitudinal study of health for the next generation*
- Maternal Cohort Data – IRBNET #1830598: *Project Viva Women's Health: A longitudinal study of women's health*

Additional protocols also contribute variables to our database.

Investigators may view and analyze only datasets that are provided to them by the Project Viva Lead Research Analyst for their approved analytic plan/grant aims. Sharing a dataset or analyzing a dataset sent by another investigator, an assay lab, or any other individual or entity is against Project Viva's policies. In addition, prior datasets must not be used for newly proposed analyses, even when approved by Project Viva's DMG.

Project Viva's data repository consists of two folders, one on Viva's section of DPM's local area network drive and one on the SAS server. They will contain SAS, Stata, CSV, and excel datasets from our data freezes. The datasets will include Viva participant ID number, but none of the 18 HIPAA identifiers (including dates) are stored in the repository. Only Viva's programmers, Data Manager, and Program Manager will have access to the data repository.

For epigenomic analyses contributing data to this repository, Project Viva biospecimen samples are labeled with study ID number, but no other identifiers. Therefore, the datasets containing results of epigenetic analyses do not contain any PHI. These datasets are stored by the Project Viva Lead Analyst in a secure, password-protected location, such as on the secure J:\ drive. De-identified epigenetic data may also be stored on the Harvard University O2 server, which is Harvard Security Level 3 data compliant. The O2 server is protected by two-factor authentication.

Project Viva's Data Manager and Lead Research Analyst are the repository administrators. They are responsible for managing access to all of Viva's folders, and for stripping identifiable information from the data prior to adding them to the repository. Viva's Program Manager, Data Manager and other staff members may not disclose identifiable information or the linking code to an outside investigator.

Project Viva's Lead Research Analyst is responsible for creating ancillary datasets from the data repository and sharing them securely with the approved external investigator. They may also assist with analyses and be an author on papers if appropriate.

Analytic *datasets* created and distributed by the Lead Research Analyst will be destroyed by the recipient investigator within one year after their manuscript(s) has been accepted for publication. If institutional policies require a different duration for maintenance of a dataset, the investigator should notify the Project Viva PI/PM for discussion and resolution of the difference in policies. This policy does not refer to *summary/tabulated results*, which the recipient may retain as needed. The one-year timeframe allows them to respond to any changes or queries post-publication.

To further safeguard participant privacy and confidentiality, the Lead Research Analyst will:

- Include only necessary variables in data sets.
- Email data sets using encryption or share through the Institute-approved instance of Box (https://point32health.app.box.com/)
- Email the data set with the below language, or send it with the Box link to the data:

  "The recipient has read Project Viva's Policies and agrees to abide by them. The recipient agrees to use or disclose the data only for the purpose requested, and for no other purpose. The recipient agrees to use appropriate safeguards to prevent any use or disclosure of the data. The recipient agrees to destroy any dataset provided by Lead Research Analyst within the time frame outlined in these policies. The recipient will report to Project Viva's Program Manager any violation of this agreement or Viva Policies."

Project Viva's Program Manager will keep documentation of all ancillary study requests and determinations. They will track the following:

- CVs and CITI certifications (or other institutional certification requirements if not CITI)
- Outside institution IRB determinations for annual review by HPHC's HSC.
- Who has been sent data sets and what variables were included. The Lead Research Analyst will copy the Program Manager on all ancillary study data set emails in order to track this.
- Documentation stating that the proposing author agrees to abide by the policies outlined in this document.

Project Viva will store sent datasets in our data repository and will destroy the data repository 6 years after the end of the study.

E. Requests for Identifying Information

If the investigator requires PHI (including dates or address) the study is not a data repository ancillary study. The investigator should follow the steps outlined in Section III.C above to propose a study that involves identifying information.

If an investigator requests a data set with PHI, the Program Manager will review and facilitate all necessary approvals, and if approved, an assigned Viva analyst/programmer will prepare an analytic data set. In many cases a new variable can be created that obviates the need for identifying information and can then add the de-identified variable to the data repository. For example, rather than providing date of birth and date of visit, we can instead provide exact age at the visit. Rather than providing addresses, we can and typically prefer to provide variables that have already been linked to the address using geocoding. If this is possible, the proposal could be considered under the repository as only de-identified data would be included.

IV. Data Analysis

The investigator can use Viva's Manuscript Checklist to ensure completion of each of the following steps before manuscript submission (Appendix I).

A. Drafting a Viva Analysis Plan

1. The proposing author will prepare an analysis proposal to be approved by the DMG. The author will present the proposal at a monthly Co-I meeting.
   a. The investigator can receive tabulated preliminary results from Viva's Lead Research Analyst to prepare the proposal.
   b. We recommend communication with a Viva biostatistician before presenting the proposal.
   c. The proposing investigator will provide the title to Viva's Program Manager at least one week before the meeting at which it will be discussed. The proposer should submit an electronic copy of the analysis plan to the Program Manager by 8am on the morning of the meeting so that copies can be made for the group as requested. The analysis plan should consist of a single power point file; tables and figures may be submitted as a supplemental file or as additional slides at the end of the presentation slides.
   d. All investigators must review the document "Guidelines for Analyzing and Reporting Project Viva Data" before they prepare their presentation.

B. Analysis Proposal Guidelines

Specific guidelines, examples of analysis proposals, presentation templates, and policy and resource documents can be found on the Project Viva Research Operations and Data Management Platform (ROADMaP).

The investigator should use the provided Power Point template to prepare the proposal. If the proposal will involve Epigenetic analyses, the investigator should refer to the Epigenetic flow documentation provided alongside the proposal template on the ROADMaP. A proposal template for Grant Aims is also available.

Bullet points are better than prose. The outline provided is not strict; proposers may modify it if it does not meet their purposes. It is typical that during a monthly co-investigator meeting, 20-25 minutes will be allocated for discussion of a given analysis plan, and perhaps a shorter time slot for grant aims. Investigators should prepare to present the analysis plan in a maximum of 10 minutes to allow time for questions and discussion.

Following approval and completion of the additional requirements listed in Section III.C above, Viva staff will provide the proposer with the data elements needed to perform the approved analysis. Statistical programming is the responsibility of the proposer unless otherwise arranged.

1. The DMG will review the proposals, offer comments, and approve them as appropriate within two weeks of the meeting. Within one week of DMG approval, should any changes have been requested since presentation, the proposer should submit a final copy of the analysis plan to the Program Manager.

2. After the DMG approves an analysis plan and before the publication process, the proposer will bring the results back to the DMG, through sharing a manuscript draft or presentation of a Data Update at a Co-I meeting or other forum (such as Viva 'omics or Viva environmental mixture meetings). Project Viva views analysis plans as works in progress. Approved plans are brought back to the DMG for results presentation, at which time the DMG will decide: 1. the results are ready for publication and the proposer shall proceed with the standard publication process with their co-authors; or 2. the analysis requires additional work.

C. Programming Review

SAS is the preferred analytic package for Project Viva analyses; Stata and R are also acceptable. Regardless of the program used, programmers must be ready to defend all procedures during statistical/programming review. Authors must send the Project Viva Lead Research Analyst their program (code) for review. We strongly encourage junior investigators or analysts that are using Project Viva for the first time to send their code early in the process (e.g. before to start writing the manuscript or present data update) to avoid having to change substantially their tables/figures and interpretation of results. The Lead Research Analyst will review all code/output with the lead author or designee prior to submission of the manuscript. The Lead Research Analyst, at their discretion, may repeat some or all of the analyses. The lead author should plan on a three-week turnaround for this step.

Programmer time is recognized as a limited resource and there will always be competing demands. In general, we prioritize requests for programmer time in the following order: 1) grants, 2) abstracts, 3) providing datasets, 4) manuscript reviews. However, circumstances will vary, and lead authors are encouraged to communicate with the programmer about deadlines as well as to find out the expected timeline. The programmer will keep an ongoing list of projects and will be able to notify the lead author about expected delivery.

If authors fail to keep their timelines, the DMG has the authority to change authorship order or inclusion.

D. Reviews: Technical, Co-Author and Departmental

1. All manuscripts must have a technical review to ensure that the data are presented accurately. In practice, the Viva Lead Research Analyst generally does this as part of the programming review. The technical reviewer will:
    a. Check for consistency and plausibility of numbers
    b. Double check tabulated numbers with primary output
    c. Ensure that numbers add correctly etc.

2. All Co-Authors on a manuscript must have both the opportunity to provide edits on the manuscript during the development phase, and also to review and sign-off on a final manuscript draft before journal submission.

3. The Chair of the Department of Population Medicine (DPM), as well as the Director of Institute Administration, must also review all manuscripts before authors submit them. Investigators should send their manuscript to coral_publications@hphci.harvard.edu, PI Emily Oken, and Lead Research Analyst. Viva's Lead Research Analyst will coordinate sending out the manuscript for these reviews, but it is ultimately the responsibility of the lead author to confirm that the paper has been sent for review. Authors should allow up to 7 working days for DPM review before submitting any manuscripts for publication; no response after this time can be considered approval.

V. Publications

A. General Guidelines for Authorship

Criteria for authorship, based on ACP/Vancouver Group guidelines, are as follows:

1. Authorship requires 3 steps:
    a. Conception of design of the work, or data analysis/interpretation, or both
    b. Drafting the article or critically important revisions
    c. Approval of the final version.

2. Participation in data collection alone does not confer authorship.

3. Authors may acknowledge persons who contributed intellectually but do not qualify to be authors.

4. Note: Some journals now focus on specific contributions rather than, or in addition to, authorship. Authors should follow the instructions of those journals.

B. The Lead Author

1. The lead author and proposing investigator are usually the same person, but not always. For example, if the analysis plan results in more than one manuscript, the proposer may not be the lead author for all manuscripts. Or in some cases, the senior author may be the proposer.

2. Responsibilities of the lead author are as follows:
    a. In consultation with the Project Viva PIs or their designee, decide on who will be authors and in what order they will be listed. The lead author will be listed first, followed in order by descending level of contribution to the manuscript. The "senior author," may choose to be last author. In support of team science, we encourage co-first authors if more than one person contributed substantially to leading all phases of the project.
    b. Perform all statistical analyses, or work with the Project Viva lead analyst or another programmer to conduct the analyses in accordance with the approved analysis plans. There may be several rounds of analyses, and the lead author should work with the senior author(s) and other coauthors to ensure that the analyses are appropriate to address the study question(s).
    c. Assign co-authors responsibility for writing specified sections of the manuscript.
    d. Write the initial draft of the manuscript. Please see Guidelines for Analyzing and Reporting Project Viva Data for Project Viva standards and best practices.
    e. Work with the senior author to revise the initial draft(s).

f. Circulate the draft to coauthors and the Lead Research Analyst for comments. (While the methods and results must be accurate, interpretation of results can differ among observers).
g. Prepare the final version, including references and formatting for the intended journal.
h. Provide the Project Viva Lead Research Analyst with copies of the programs (code) used to generate each value in the text and tables.
i. Complete the process within the specified timeline.
j. Update the Project Viva Program Manager on the status of the manuscript. Provide a copy of the final accepted manuscript to the Program Manager.
k. Once accepted for publication, provide the official citation and the final manuscript including all supplemental materials to coral_publications@hphci.harvard.edu.
l. Ensure that the publication is compliant with PubMed Central requirements.

C. Senior author

1. The senior author is the person who took primary responsibility for supervising or working with the lead author and is often (but not always) the PI of the grant that funded the work, or the primary mentor of the student leading the work. The senior author is responsible for ensuring that both the analysis and the manuscript that result from it are high quality and in accordance with Project Viva standards and best practices. The senior author should be the first person to review the draft manuscript and decide when it is ready to be shared with the other authors.

2. Typically, the senior author is listed last in authorship order. We encourage co-senior authors if more than one person contributed substantially to this role, e.g., if there were MPI's of a grant.

D. Coauthors

1. As part of fulfilling their roles as authors, coauthors will read and provide critical input to the entire manuscript; they may be asked to write the first draft of assigned sections of the manuscript.

2. The lead author and Lead Research Analyst are responsible for checking all numbers in text and tables.

E. Project Staff as Authors

Publications are one currency of academia, and faculty investigators will have first choice to be authors. The primary responsibilities of staff are to implement project activities. In certain analyses, however, staff members may make sufficiently substantive contributions to warrant co-authorship. Assuming no

interference with primary job duties, we will also support staff members to lead analyses when the topic is of interest and no faculty investigator wishes to be lead author. The staff member performing the analysis must first make a formal request to the Lead Research Analyst for the dataset to analyze; the Lead Research Analyst will determine whether it is acceptable for the staff member to pull their own data set, or whether the Lead Research Analyst will do it. The staff member also must abide by all Viva policies.

F. Abstracts and Presentations

1. We strongly support presenting scientific abstracts and other talks about Project Viva because they jump-start the analytic process, allow the presenter to obtain valuable feedback, promote networking, and publicize the work of Project Viva.

2. Responsibilities of the lead author of a scientific abstract are as follows:
    a. Obtain approval of the analysis plan, as outlined above. If the abstract submission date is imminent, the DMG can decide to give preliminary approval for the abstract only, but will require full approval before manuscript analyses proceed.
    b. Draft the initial abstract, paying close attention to the detailed submission instructions.
    c. Circulate to coauthors and the Viva PI and Co-PI for comments. We suggest circulating the abstract at least two weeks in advance of the submission deadline to allow for any needed revisions.
    d. Send programming code to the Project Viva Lead Research Analyst. They will review all code/output with the lead author or designee prior to submission of the abstract. The Lead Research Analyst, at their discretion, may repeat some or all the analyses. The lead author should plan on one week turnaround for this step.
    e. Keep the co-authors, Viva PI, Co-PI, and Lead Research Analyst updated on the status of the abstract.
    f. Once selected, circulate the abstract to the coauthors and coral_publications@hphci.harvard.edu.

3. Ideologically, we will support interested project staff to present abstracts at scientific meetings. Funding for travel and registration may be limited, but we will offer it when it is available.

Project Viva Contact Information

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Appendix I: Analysis Plan and Manuscript Checklist

Use this checklist to keep track of all steps involved with moving your analysis plan through to an approved manuscript.

Analysis Plan Approval:

- Analysis plan presented at a Co-I meeting and approved by Viva's DMG ☐
- Analysis plan approved by HPHCI's IRB, or if covered under the data repository or genetics repository protocols approved or determined exempt by the lead investigator's local IRB ☐
- CITI certification complete and submitted to Viva Program Manager ☐
- Confirmation of approval by your IRB or documentation of a NHS determination submitted to Viva Program Manager ☐
- Final analysis plan submitted to Viva Program Manager ☐
- Data transfer agreement signed (if required) ☐
- Data update presented at a Co-I Meeting ☐

Program Review:

- Program (code) submitted to Viva's Lead Research Analyst for programming review ☐
- All results presented in the paper reviewed by Viva's Lead Research Analyst ☐

Co-author and Technical Review:

- Technical review of the manuscript complete ☐
- Manuscript reviewed and approved by all co-authors ☐
- Appropriate Viva grants cited in the manuscript ☐

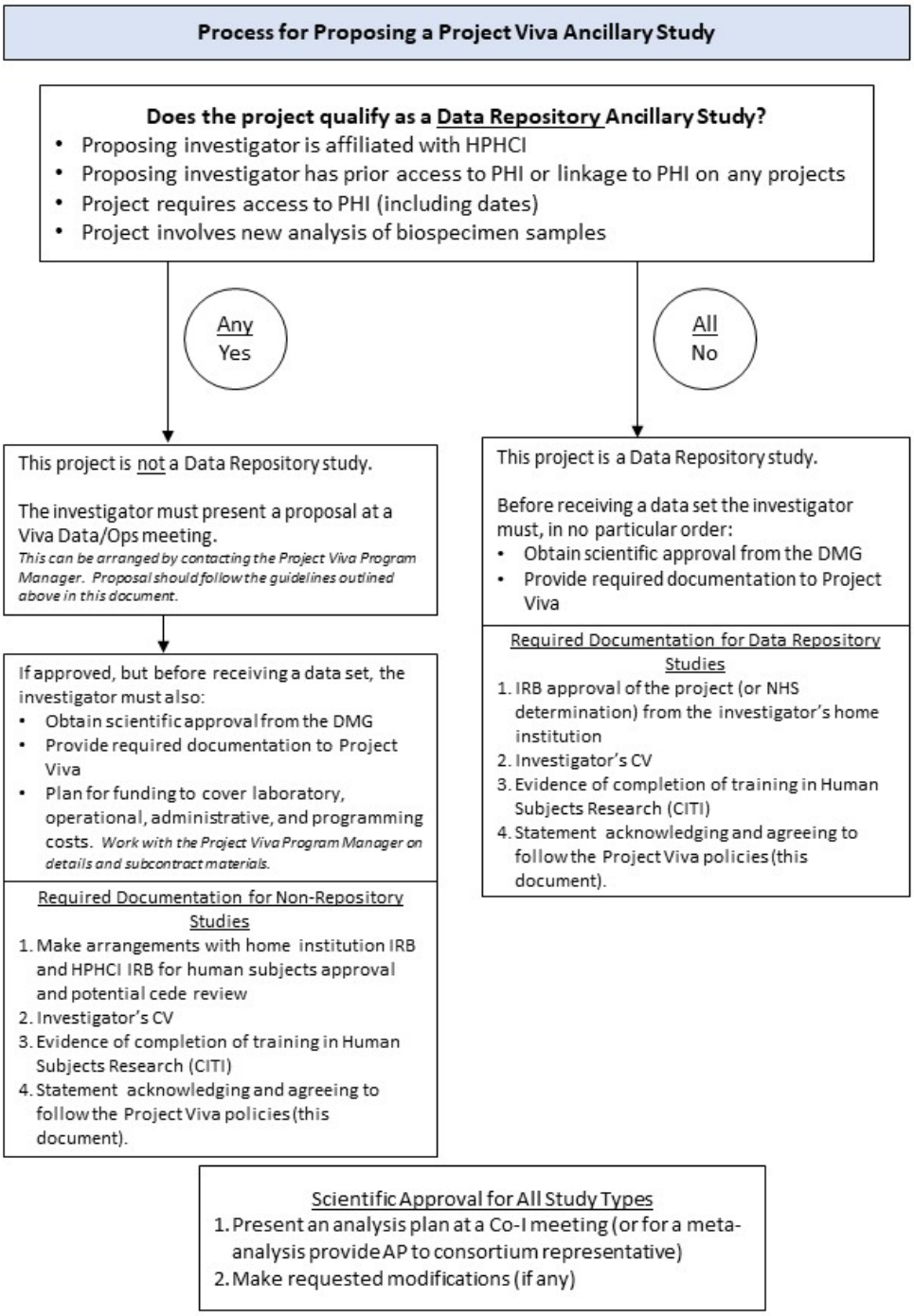
Departmental Review:

- Manuscript submitted for DPM review ☐

Publication Tracking:

- Final copy of submitted manuscript provided to CoRAL Publications and Viva PIs ☐
- After acceptance, publication compliant with PubMed Central requirements ☐

Appendix II: Flow Chart of Ancillary Project Proposal Process



Appendix III: Budgeting Guidelines for Proposed Ancillary Project

Funding through a subcontract to HPHCI will always involve the following preparation of the following documentation:

- SPA
- IRB
- DTA
- Budget & justification
- 398 Checklist
- Statement of Intent
- PHS 398 Face Page
- Statement of Work
- FCOI

The Proposed Project Involves…	Staff Effort to Include in Budget	Other Items to Include in Budget
New assays on existing biospecimen samples	PM, Programmer	Lab storage and processing fees
New data collection	OpsM, RAs	Mailing costs, incentives, supplies
Data collection from Viva participants	+ DM, PM	
New biospecimen collection from Viva participants	+ PM	Lab storage and processing fees
PHI (including dates) or information on sensitive topics	PM	
Complex analysis or programming to identify participants/samples or create datasets	Programmer	

Abbreviations Used Above

DTA = Data Transfer Agreement *(will include an addendum for projects that involve biospecimen samples)*

DM = Data Manager

IRB = Institutional Review Board

FCOI = Federal Conflict of Interest

PM = Program and/or Project Manager

OM = Operations Manager

SPA = Sponsored Programs Application

Appendix IV: Guidelines for use of the Project Viva Biospecimen Samples

A. Rationale

The biospecimen samples collected from Project Viva participants represent a finite and precious resource. We must be careful to use them in the most productive and efficient ways as possible, lest we lose opportunities to address the most important scientific hypotheses. We also would like to use them efficiently so as to require the least storage space and least number of thaws as possible.

In addition, we would like to be cognizant of potential future hypotheses when we use our samples. These hypotheses will point us toward sampling frames that result in sample selections that can be used repeatedly, again reducing the need to use more biospecimen samples than necessary.

B. Project Viva Biospecimen Sampling Protocols

Mom, 1st trimester -10 ml EDTA purple top and 10 ml Heparin green top
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.5-ml plasma from both purple top and green top tubes (4 total)
- 2 1-ml RBC from purple top tube
- 1 WBC pellet for DNA from purple top tube

Mom, 2nd trimester -10 ml EDTA purple top and 10 ml Heparin green top
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.5-ml plasma from both purple top and green top tubes (4 total)
- 2 1-ml RBC from purple top tube only
- 1 WBC pellet for DNA from purple top tube

Mom, birth – hair
We collected hair on a subset of participants (n = 411). We store hair at Project Viva's office.

Mom, early childhood visit – 10 ml EDTA purple top and 10 ml Heparin green top
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.5-ml plasma from both purple top and green top tubes (4 total)

- 2 1-ml RBC from both purple top and green top tubes (4 total)
- 1 WBC pellet for DNA from purple top tube

Mom, mid-life (mid-teen) visit

1. Blood - 10 mL EDTA purple top tube and 10 mL Heparin green top tube

Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 500µL, 1 800µL, 1 1.8mL plasma green top tubes
- 2 1.8mL RBC green top tubes
- 1 700µL, 500µL, 1 300µL, 3 100µL, 1 1.8mL plasma purple top tubes
- 1 1.8 mL whole blood purple top tube
- 1 WBC pellet for DNA from purple top tube only

2. Blood – (2) 4mL gray top tubes. whole blood transported to Boston Children's Hospital within 24 hours from collection for processing:

- 4mL gray top tube (fasting glucose)
- 4mL gray top tube (2-hours post OGTT)

3. Urine – 30 mL Conical Tube containing urine

Transported to Channing within 48 hours (with few exceptions)
Spun and aliquoted there into:

- 6 1.8-mL aliquots, frozen and stored

Child, cord blood – 3 10 ml Heparin green top (for cell proliferation work), 1 10 ml red top, 1 10 ml EDTA purple top
Whole blood transported to Channing within 12 hours
Spun and aliquoted there into:

- No plasma or RBC from green top tube, all cell pellets and supernatants from proliferation work
- 2 1.5-ml plasma from purple top tube
- 1 WBC pellet for DNA from purple top tube
- No RBC collected
- 2 1.5-ml serum from red top tube

Child, early childhood visit

Main Cohort

2 ml EDTA purple top*****, 6 ml Heparin green top and 4 ml EDTA purple top
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.5-ml plasma from green top tube
- 2 1-ml RBC from green top only tube
- 1 1.5-ml plasma from purple top tube
- 1 WBC pellet for DNA from purple top tube only

Immune Substudy

1. Blood - 2 ml EDTA purple top***,** 6 ml Heparin green top (kept at room temperature prior to processing), and 6 ml Heparin green top (kept cold prior to processing)
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.5-ml plasma from each green top tube (4 total)
- Stimulation supernatants (from Bla g 2, Der f1, Fed d1, PHA and Media) from 'room temperature' green top
- 2 1-ml RBC from 'cold' green top

****** *2 ml purple top processed at HVMA for CBC. If child HVMA patient processed for lead too.*

2. Dust - Collected from bed and floor area of child's room.

Child, mid-childhood visit

1. Blood – 10 ml EDTA purple top, 10 ml Heparin green top, 2 ml grey top
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.5-ml plasma green top tube
- 2 1.5-ml RBC green top tube
- 2 1.5-ml plasma purple top tube
- 2 1.5-ml RBC purple top tube
- 1 WBC pellet for DNA from purple top tube only
- Grey top for glucose assay

2. Urine
Transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 10 1-ml aliquots, frozen and stored

3. Hair - We store hair at Project Viva's office.

Child, early teen visit
1. Blood – 10 ml EDTA purple top, 10 ml Heparin green top, 2 ml grey top
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 1.8ml plasma green top tubes
- 2 1.8-ml RBC green top tubes
- 2 1.8-ml plasma purple top tubes
- 2 1.8-ml RBC purple top tubes
- 1 WBC pellet for DNA from purple top tube only
- Gray top for glucose assay

2. Urine
Transported to Channing within 48 hours (with few exceptions)
Spun and aliquoted there into:

- 10 1.8-ml aliquots, frozen and stored

3. Hair - We store hair at Project Viva's office.

Child, mid-teen visit
1. Blood – 10 ml EDTA purple top, 10 ml Heparin green top, 2.5 mL PAXgene Blood RNA Tube
Whole blood transported to Channing within 24 hours (with few exceptions)
Spun and aliquoted there into:

- 2 500µL, 1 800µL, 1 1.8mL plasma green top tubes
- 2 1.8mL RBC green top tubes
- 1 700µL, 500µL, 1 300µL, 3 100µL, 1 1.8mL plasma purple top tubes
- 1 1.8 mL whole blood purple top tube
- 1 WBC pellet for DNA from purple top tube only

1 2.5mL PAXgene Blood RNA tube2. Blood – 4mL purple top tube, 4mL gray top tube. Whole blood transported to Boston Children's Hospital within 24 hours from collection for processing:

- 4mL gray top (fasting glucose)
- 4mL purple top (CBC w/diff)

2. Urine - 30mL Conical Tube containing urine
Transported to Channing within 48 hours (with few exceptions)
Spun and aliquoted there into:

- 6 1.8-ml aliquots, frozen and stored

3. Hair - We store hair at Project Viva's office.

C. Requirements for Proposing an Ancillary Study Involving Biospecimen Samples

Investigators wishing to propose an ancillary study involving the use of Project Viva biospecimen samples should follow the procedures outlined in section III.C. of this document. The investigator should consider the following requirements when preparing an ancillary study proposal:

To be useful, a biomarker should have acceptable laboratory and biological characteristics. Before Project Viva will approve a proposal, the proposing investigator needs to address each of the following issues satisfactorily.

1. Laboratory factors:

   a. Stability in whole blood refrigerated up to 24 hours. The proposer needs to demonstrate that our collection techniques do not result in degradation of the assayed biomarker.
   b. Appropriateness of samples collected in either sodium heparin (green), EDTA (purple), or untreated (red) tubes. The proposed lab needs to confirm that they routinely accept these color tubes for the assay of interest. Otherwise the proposing investigator must arrange a pilot study to establish that the diluent will not interfere with the assay.
   c. Minimal volume needed to perform the assay. Because of the scarcity of the samples, the assay needs to be done on as small a volume of plasma as possible. Investigators have often had the experience of "bargaining" the lab down to smaller volumes than the original offer, especially by contacting several labs or comparing different assays. The maximum allowable volume will depend on the importance of the hypothesis under study. Having one lab perform multiple tests on one sample with minimal volume is desirable.

d. Reproducibility of the assay. The lab must be able to conduct the assay with a high degree of precision, usually measured by the coefficient of variation. As a guide, a CV of over 10% is usually not acceptable. The gold standard for obtaining the CV would be a blinded evaluation on a reasonable sample size within the previous 6 months. They should not solely rely on the reported values of the lab, since the reported values are often based on samples not representative of the study population and can wildly overestimate precision. Some of the factors that the proposer should take into consideration when determining the reliability of the laboratory's evaluation of reproducibility include the age of the subjects from which samples were collected and the sample volume used.

2. Biological characteristics:

a. Between-person variability (want to maximize). The proposer must show data, either from Viva or another population of pregnant women or children, which demonstrate a large enough range among the study sample to ensure adequate power for the question under study. If the biomarker is during pregnancy, because we have samples from early and late pregnancy the proposer should address timing during pregnancy; for example, some biomarkers may have a wider range later in pregnancy than earlier. We have stored plasma samples from the Viva pilot study (Pregval) collected from over 200 women at the end of the first trimester. If investigators show that all other criteria are met, and only this one remains, investigators may—with the permission of the Viva decision-making group—use these samples to address the range of the biomarker in the late first trimester. Variability may also depend on the participant age at sample collection (cord blood, early childhood, mid-childhood, early teen).
b. Within-person variability (want to minimize). Also known as how well a single measure represents the "true" level. In Project Viva, for example, only one, non-fasting, sample is available from each of the first two trimesters of pregnancy and one sample (generally fasting) from each of the in-person child visits. Data should be available to show that assay of a single blood sample will provide a sufficiently integrated measure of the desired exposure or outcome that associations are detectable if they exist.

3. Sample Selection:

The investigator also needs to work with Viva's Lead Research Analyst to select the samples, with due consideration for how this sampling may affect future Viva analyses. The proposer should include the sampling scheme in the proposal presented at a Viva Data/Ops meeting, and the Viva PIs and Lead Research Analyst must sign off on the selection programs before the lab retrieves specimens.

D. Study Costs

Investigators using the biospecimens must provide funds to cover the following costs:

1. Initial programming needed to identify samples; retrieving, aliquoting, and shipping of specimens; receiving and cataloguing of returned specimens; data entry of results; and additional freezer space necessitated by the aliquoting of samples. Some of these costs will be charged by Project Viva and others will be charged directly by the Project Viva biorepository.

2. In parallel with the laboratory analysis of samples, (a) a test of laboratory reproducibility immediately prior to submitting any study samples if the previous assessment occurred 6 or more months in the past, including updates of reproducibility if the assay is performed over time in more than 1 batch, and (b) quality control specimens to be analyzed along with the study samples (in approximately a 1:10 ratio).

3. If required, pilot studies to determine the feasibility and validity of the proposed project.

4. As with any Viva ancillary project, project and data management and programming time.

The Project Viva Program Manager can provide investigators with an estimate of the operations-related costs to assist with budgeting and ensuring availability of sufficient funds. Costs associated with the investigator's chosen assay lab, as well as assay reproducibility and pilot costs, should be obtained directly from the lab.

E. Data Management

The Viva program or data manager will track all projects using biospecimens. The information will include:

a. the hypothesis, definitions of exposures and outcomes,
b. the information about the assay as described in part C. above,
c. the process to select samples, including study design and any matching factors (if applicable),
d. the timeline for completing the project,
e. the blood samples used, including volumes, and remaining volume after use

F. Outside Investigators

These policies are meant to apply to funded Viva investigators, not to investigators unaffiliated with Project Viva. If outside investigators wish to use the Viva resource, the decision-making group will take up each request on an ad hoc basis.