Project Viva Policies

Grant Applications, Analyses, Ancillary Studies and Publications/Authorship

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 will probably be so for some time to come. 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.

I. Decision-Making Authority

Collaboration and participation are the underlying principles. The Viva PI 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 PI has 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 to a lesser extent. In addition to being listed as a PI or Co-I, one must also be actively involved with the Co-I meetings and operations. Project Viva Co-Is are listed in the study protocol for *235301: Project Viva: A longitudinal study of health for the next generation [https://www.hms.harvard.edu/viva/protocol-viva-full.pdf]*. Every year at the time we resubmit our protocol to the Harvard Pilgrim Health Care IRB, the Viva Program Manager, in conjunction with the PI and Co-PI, will annually review the Co-Is listed on the protocol. 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 June 2020) is as follows:

1. Pre- and Peri-natal Predictors of Childhood Obesity (Oken PI)
2. The Fetal and Childhood Environment, Oxidative Balance, Inflammation and Asthma (Gold and Oken PIs)
3. Common and distinct early environmental influences on cardiometabolic and respiratory health: Mechanisms and methods (Oken and Kleinman, PIs)
4. A lifecourse approach to women's cardiometabolic and bone health: from fertility to perimenopause (Oken and Chavarro, PIs)
5. Long-term health consequences of birth by cesarian section (Chavarro and Oken, PIs)
6. Environmental Chemicals, Adiposity, and Bone Accrual across Adolescence (Fleisch and Oken, PIs)

7. Physiologic and social stressors and health during the menopausal transition (Oken and Chavarro, PIs)
8. Maintain and Enrich Resource Infrastructure for Project Viva: a pre-birth cohort with follow up into adolescence (Oken, PI)

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.

Investigators wanting to write grants to fund Viva-related activities must first communicate with the PI and the Program Manager. Because virtually all grants require staff time and some also lead to additional participant burden or involve bioassays, and to ensure that the proposal will not interfere with or duplicate ongoing activities, the investigator should first plan to attend a Data/Operations meeting to discuss the administrative and budgetary implications. The investigator should contact the Program Manager to arrange this. Please see below under Viva Ancillary Studies → Other Ancillary Studies → Process for Proposing a Project Viva Ancillary Project for more information. Once approved by Viva Data/Operations, the investigator will present the proposed analysis at a Co-I meeting to discuss the scientific worth of the idea. 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.

All ancillary grants should include a Harvard Pilgrim Health Care Institute (HPHCI) Project Viva investigator as a co-investigator or possibly PI on the grant. The proposer may be the PI, 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.

We will support junior investigators to become more independent by looking for opportunities for them to become PIs on Viva-related grants.

III. Viva Ancillary Studies

A. Overview

As time progresses, Viva's data set grows and scientific knowledge evolves. We now have over 16 years of data which easily 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. Due to this rich nature of Project Viva's data set, there has been an increase over the past several years in requests to use Viva data for ancillary studies.

B. Ancillary Study Definition

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 and who is not currently listed as a Co-I on a Project Viva protocol. If a study meets all criteria for a data repository ancillary study, no HPHC IRB review is required. A study that involves a topic or data of a sensitive nature (e.g. mental health, genetics, drug/alcohol use, fertility, STDs, HIV status, etc.) or 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.

a. Participation in Research Consortia

Project Viva is presented with an increasing number of opportunities to contribute its data to various research consortia. Consortium-based studies that involve a topic or data of a sensitive nature, as outlined above, do not qualify as data repository ancillary studies.

For consortium-based studies, the lead investigator may request pre-existing, de-identified Project Viva data on all or part of the cohort. These data may be requested in tabulated form, or in some cases, as individual-level data. The proposing investigator will communicate their request and will provide an analysis plan to Project Viva's consortium representative, a qualified individual identified by Project Viva to act as a liaison to the consortium. The Project Viva consortium representative will provide a copy of the data request and analysis plan to Project Viva's PI, Dr. Emily Oken, 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. If the investigators approve Project Viva's contribution to the proposed analysis, the consortium representative will communicate a request for data and deadlines to Project Viva's Program Manager, Data Manager, and Lead Research Analyst. The Program Manager will be responsible for tracking all projects

and required documentation, and the Lead Research Analyst 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 Lead Research Analyst provides the requested dataset.

b. Collaboration with Independent, External Investigators Conducting Meta-analyses

Independent, external investigators conducting meta-analyses may request pre-existing, de-identified Project Viva data on all or part of the cohort. These data may be requested in tabulated form, or in some cases, as individual-level data. The proposing investigator will communicate their request and will provide an analysis plan to Project Viva's PI, Dr. Emily Oken, 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. If the Viva investigators approve Project Viva's contribution to the proposed analysis, the proposing investigator will communicate a request for data and deadlines to Project Viva's Program Manager and Lead Research Analyst. The Program Manager will be responsible for tracking all projects and required documentation, and the Lead Research Analyst 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 investigator before the Lead Research Analyst provides the requested dataset.

ii. Other Ancillary Studies

Other types of ancillary studies, such as a research plan that requests Protected Health Information (PHI) or medical records, grant proposals to fund data collection, or requests for biospecimen samples to analyze, are also welcomed and encouraged. However, the investigator must consider additional issues of consent, IRB approval, participant burden, operations, funding and future plans. Investigators should use these guidelines to create proposals and budgets for their projects:

C. Process for Proposing a Project Viva Ancillary Study

We encourage outside investigators and collaborators to propose 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 either: 1) approve the analysis plan or 2) recommend that the proposing author revise the plan and present again at a future meeting.

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: http://connects.catalyst.harvard.edu/regulatoryatlas/?mode=c&id=5.) The proposing investigator should provide the Project Manager with either: 1) documentation of IRB approval, or 2) a letter or e-mail 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.

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

In addition, we invite all investigators proposing a project that does not fall under the Viva Data Repository to first attend a Project Viva Data/Operations meeting to present a 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
    - Identification of study sample and inclusion/exclusion criteria, if applicable
    - Information about any requested biosamples, including visit, N, and volume (see policies for biospecimen sample use in Appendix V)
    - 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 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 Operations team, the proposing investigator then 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 to reduce burden on Project Viva staff. Documents will include:
    - Research protocol for the IRB
    - Up-to-date list of all outside staff involved in handling samples/viewing data
    - CITI training certificates and CVs for all staff and investigators
    - IRB approval from the investigator's home institution, or a Cede Review Request form and confirmation that the home IRB agrees to a cede. Investigators considering requesting to cede review should first discuss this with the Project Viva Program Manager.
    - 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 separate HPHC IRB review, as well as a data sharing agreement (DUA or DCA). If the study involves analysis of Project Viva biospecimen samples, a Data and Samples Transfer Agreement (DSTA) will also be required. The investigator should allow 1-2 months for completion of all of these requirements, although this is also dependent on the requirements of the investigator's institution.

After all of the above requirements are met, the investigator may request a dataset from the Lead Research Analyst. The Program Manager should be copied on this request. 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. He/she may use the data only for purpose originally requested. Approval must be granted by Viva's DMG and the HPHC IRB, as required, for additional use of the data.

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 and mailed visits approved under protocol *235301: Project Viva: A longitudinal study of health for the next generation* [https://www.hms.harvard.edu/viva/protocol-viva-full.pdf]. **Additional protocols** also contribute variables to our database.

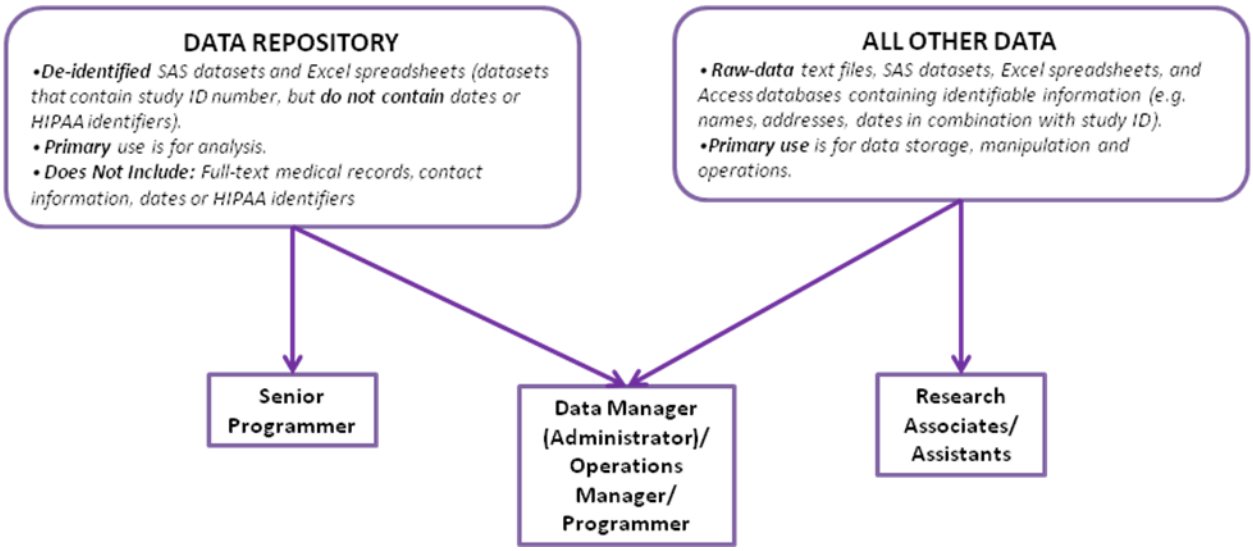
Investigators may view and analyze only datasets that are provided to them by the Project Viva Lead Research Analyst. Sharing a dataset or analyzing a dataset sent by another investigator, a lab, or any other individual or entity is against Project Viva's policies. In addition, old datasets should not be used for newly proposed analyses.

Project Viva's data repository will consist of a folder on Viva's section of DPM's local area network drive. It will contain SAS and excel datasets from our most recent data freeze. The datasets will include Viva 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.

Project Viva's Data Manager will be the repository administrator. He/she will be 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 member 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 sending securely to the IRB-approved external investigator. He/she may also assist with analyses and be an author on papers if appropriate.

Ancillary *datasets* created and distributed by the Lead Research Analyst will be destroyed by the recipient **investigator within one year after their final manuscript has been accepted for publication;** this policy does not refer to *summary results*, which the recipient may retain as needed. The one-year timeframe allows him/her to respond to any changes or re-run analyses based on the initial manuscript review.



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

- Include only necessary variables in data sets.
- Email data sets using encryption.
- Email the data set with the below language.
  "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 a database of all ancillary study requests and determinations. As part of this database he/she will track the following:

- CITI certification.
- 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 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 information on sensitive topics for the analysis, 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.

All requests for identifying information will be handled by Viva's Data Manager. In many cases the Data Manager will create a new variable and add the de-identified variable to the data repository. For example, one can calculate a request for age at a visit by subtracting the visit date and date of birth.

IV. Data Analysis

All proposed analyses must be approved by the DMG and HPHC's IRB as appropriate. Investigators must also seek IRB approval from their home institution. The investigator can use Viva's Manuscript Checklist to ensure completion of each of the following steps before manuscript submission (Appendix II).

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 de-identified, tabulated preliminary data 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 email 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. The analysis plan should consist of a single document (including all tables and figures) with page numbers.

2. Analysis Proposal Guidelines

    Specific guidelines and examples of analysis proposals can be found on the investigator website: http://www.hms.harvard.edu/viva/.

    Username: investigator
    Password: Johnsnow1

    The investigator should use the provided Power Point template to prepare the proposal, which should include the following elements:

    1. Background
        a. Importance of the topic
        b. Prior literature
        c. Need for new study
    2. Aims
    3. Theoretical model, including a schematic
    4. Hypotheses
    5. Preliminary work (if any)
    6. Methods
        a. Subjects
        b. Measures
            i. Outcomes
            ii. Exposures
            iii. Covariates
        c. Data analysis plan, including table shells
    7. Potential limitations
    8. Proposed meeting for abstract, if applicable

9. Proposed authors
10. Proposed timeline, including identifying the appropriate "data freeze."

Bullet points are better than prose. The outline 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. Investigators should prepare to present the analysis plan in a maximum of 10 minutes in order 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. Project Viva staff will perform the programming if the proposed analysis is closely related to a specific aim of a funded grant, assuming that programmer time is supported by the grant.

3. 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, the proposer should submit a final copy of the analysis plan to the Program Manager.

4. After the DMG approves an analysis plan and before the publication process, the proposer will bring the data back to the DMG, usually through presentation of a Data Update at a Co-I meeting. Project Viva views analysis plans as works in progress. Approved plans are brought back to the DMG for data 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.

B. Programming Review

SAS is the preferred analytic package. Programmers may use other programs if SAS does not offer the appropriate routine, but they must be ready to defend all procedures during statistical/programming review. Authors must send the Project Viva Lead Research Analyst their program for review. 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) 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.

C. 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 name of the technical reviewer should be included in all email communications. 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. The Director of Research at Atrius's Office of Clinical Research and 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 the Project Viva Program Manager, 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 7 working days for DPM/Atrius review before submitting any manuscripts for publication; no response after this time can be considered approval. To promote collaboration within the group and shared knowledge of ongoing work, we will circulate the abstract of the submitted paper to the faculty (and staff) of the DPM's Obesity Prevention Program, with the disclaimer, "Draft—please do not cite or circulate". If for some reason the lead author does not wish to have the abstract circulated to the wider group, they should inform the Lead Research Analyst.

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.

2. Responsibilities of the lead author are as follows:
    a. In consultation with the Project Viva PI, co-PI 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," typically the PI of the grant that primarily funded the work or the person who supervised the lead author, may choose to be last author.
    b. Assign co-authors responsibility for writing specified sections of the manuscript.
    c. Write the initial draft of the manuscript. We prefer active to passive voice and estimation/confidence intervals to p-values/statistical significance.
    d. Circulate the abstract to coauthors and the Lead Research Analyst for comments. (While the methods and results must be accurate, interpretation of results can differ among observers).
    e. Prepare the final version, including references and formatting for the intended journal.
    f. Provide the Project Viva Lead Research Analyst with copies of the programs used to generate each value in the text and tables.
    g. Complete the process within the specified timeline.
    h. Update the Project Viva Program Manager on the status of the manuscript. Provide a copy of the final accepted manuscript to the Project Manager.
    i. Once accepted for publication, circulate the final manuscript to the DMG and Project Viva's Program Manager.
    j. Ensure that the publication is compliant with PubMed Central requirements.

C. Coauthors

1. As part of fulfilling their roles as authors, coauthors will 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.

D. 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 make a formal request to the Lead Research Analyst for the dataset to analyze; he/she is not permitted to pull their own data set. The staff member also must abide by all Viva policies.

E. 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 get comfortable in the situation and 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 her discretion, may repeat some or all of the analyses. The lead author should plan on one week turnaround for this step.
    e. Keep the co-authors, Viva PI, Co-PI, and Program Manager updated on the status of the abstract.
    f. Once selected, circulate the abstract to the coauthors and Project Viva's Program Manager.

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 Staff Contact Information

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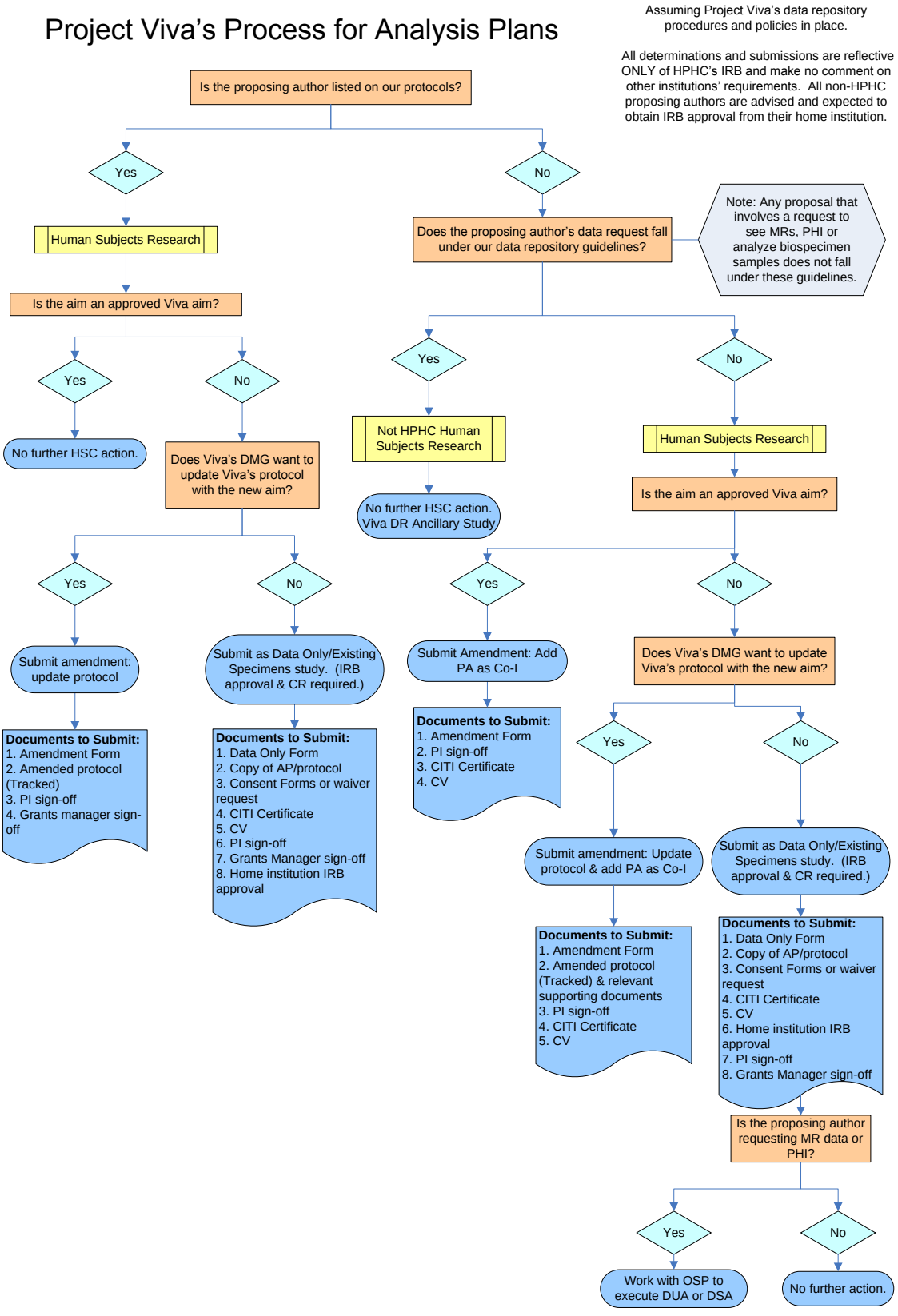
Sarah Cohan	Program Manager	Sarah_Cohan@hphc.org	617-867-4968

Appendix I: Analysis Plan Process



Appendix II: 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:

1. CITI certification complete and sent to Viva's Program Manager? Yes ☐ No ☐
2. Analysis plan presented at a Co-I meeting and approved by Viva's DMG? Yes ☐ No ☐
3. Analysis plan approved by the HPHC's HSC? Yes ☐ No ☐
4. Confirmation of approval by your IRB sent to Viva's Program Manager? Yes ☐ No ☐
5. Final analysis plan submitted to Viva's Program Manager? Yes ☐ No ☐
6. Data sharing agreements signed (if required)? Yes ☐ No ☐ N/A ☐
7. Data update presented at a Co-I meeting? Yes ☐ No ☐

Program Review:

8. Program submitted to Viva's Lead Research Analyst for review? Yes ☐ No ☐
9. All primary data presented in the paper reviewed? Yes ☐ No ☐

Co-author and Technical Review:

10. Technical review of the manuscript done by one Co-author or Senior Programmer? Yes ☐ No ☐
11. Manuscript reviewed by all co-authors? Yes ☐ No ☐

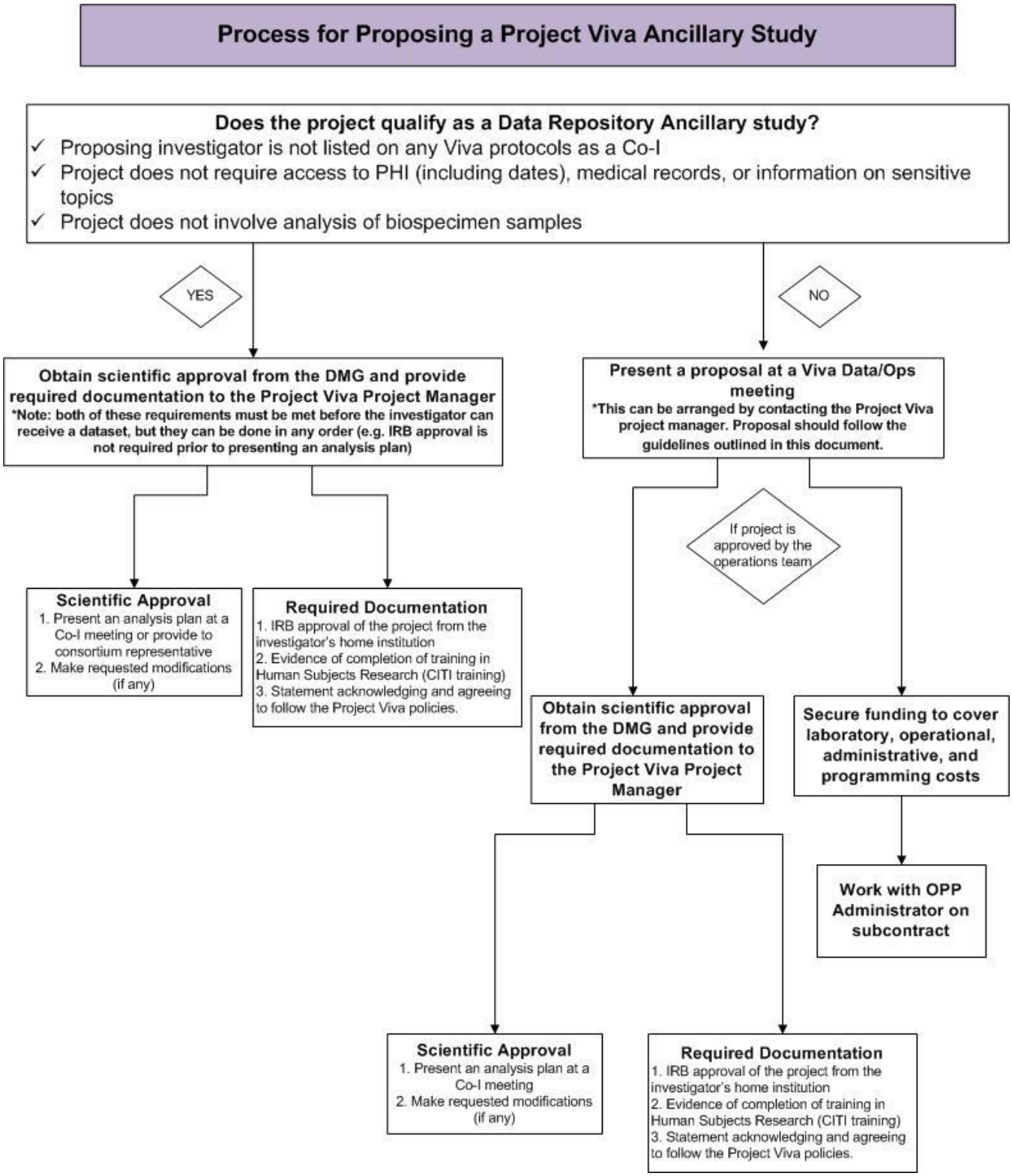
Departmental Review:

12. Manuscript submitted for Atrius review? Yes ☐ No ☐

Publication Tracking:

13. Final copy of manuscript provided to Viva Program Manager and PI? Yes ☐ No ☐
14. Publication compliant with PubMed Central requirements? Yes ☐ No ☐

Appendix III: Flow Chart of Ancillary Project Proposal Process



Appendix IV: Budgeting Guidelines for Proposed Ancillary Project

The Proposed Project Involves…	**HPHCI Requirements**	**Staff Effort to Include in Budget**	**Other Items to Include in Budget**
New assays on existing biospecimen samples	SPA, IRB, MTA, DUA/DCA	PM, Programmer	Lab storage and processing fees
New data collection		RAsc, RAs	Mailing costs, incentives, supplies
Data collection on a subset of Viva participants	SPA, IRB, DUA/DCA	+ DM, PM	
Data collection that does not fall under Viva aims	SPA, IRB, DUA/DCA	+ PM	
PHI (including dates) or information on sensitive topics	SPA, IRB, DUA/DCA	PM	
Funding through a subcontract	SPA, IRB, DUA/DCA, Budget, Budget Justification, 398 Checklist, Statement of Intent, PHS 398 Face Page, Statement of Work, FCOI	PM	
Complex analysis or programming to identify participants/samples or create datasets		Programmer	

Abbreviations Used Above

DCA = Data Confidentiality Agreement
DM = Data Manager
DUA = Data Use Agreement
FCOI = Federal Conflict of Interest
IRB = Institutional Review Board
MTA = Materials Transfer Agreement
PM = Program Manager
RAsc = Research Associate
SPA = Sponsored Programs Application

Appendix V: Guidelines for use of the Project Viva Bio-specimen samples

July 2014

A. Rationale

The biospecimen samples collected from Project Viva participants represent a finite 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 (visit 1) -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 (visit 2)-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 (visit 3) – hair
We collected hair on a subset of participants (n = 411). Hair is stored in Emily Oken's office.

Mom, age 3 or "early childhood" (visit 7) – 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 teen

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. 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 (visit 3) —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, age 3 or "early childhood" (visit 7)
<u>Main Cohort</u>
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

<u>Immune Substudy</u>
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. Stored at Channing?

Child, age 7 or "mid childhood"
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
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
1. Blood – 10 ml EDTA purple top, 10 ml Heparin green top, 2.5 mL PAXgene Blood RNA Tube, 4mL gray 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
- 1 2.5mL PAXgene Blood RNA tube

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 B.ii. 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 small sample 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 sample, 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, aliquotting and shipping of specimens; receiving and cataloguing of returned specimens; data entry of results; and additional freezer space

necessitated by the aliquotting of samples. Some of these costs will be charged by Project Viva and others will be charged directly by the lab conducting the assays.

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 specimen processing and shipping 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 and provide this information to investigators through the Viva website. 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 and programs used to generate samples, including any matching factors,
d. the timeline for completing the project,
e. the blood samples used, including volumes, and remaining volume after use,
f. the main results.

F. Other Requirements

In addition to the above, analyses using samples must follow established Project Viva policies for all data analyses (see Analysis Plans in the Project Viva policies for grants and analyses).

G. 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. Should these requests become frequent, we will modify these policies accordingly.