National Cancer Institute

EPPT – Early Phase Prevention Trials

Polices & Procedures

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1. Background

1.1. The Early Phase Prevention Trials (EPPT) Study

The Division of Cancer Prevention conducts systematic early clinical development of promising preventive agents through its **Phase 0/I/II Cancer Prevention Clinical Trials Program**, consisting of the Consortia for Early Phase Prevention Trials and the Cancer Prevention Clinical Trials Network (CP-CTNet) (view on cancer.gov). Cancer prevention drug discovery is identifying many new agents, including an increasing number of agents that intervene in specific molecular pathways thought to be critical to cancer development. Since cancer prevention studies focus on high-risk populations that do not necessarily harbor a detectable cancer, these studies require extensive biomarker analysis, investigation of the biologic effects of the cancer preventive agents on their intended molecular targets, and correlation with clinically relevant endpoints.

1.2. EPPT Study Participants

Information for each EPPT Study participants can be found on the enrollment tab for each trial located at https://cdas.cancer.gov/learn/eppt/browse/ .

1.3. EPPT Study Data Elements

Data currently available for research can be found under the datasets tab for each trial located at https://cdas.cancer.gov/learn/eppt/browse/ .

2. EPPT Biospecimens Resource Descriptions

The biospecimens collected for each trial can be found under the biospecimens tab for each trial located at https://cdas.cancer.gov/learn/eppt/browse/ .

3. Policies for Access to EPPT Biospecimens and Data

- The EPPT Biospecimen resource is available to the entire scientific community. Access to the biospecimens and associated data is based on a peer review process. Details of the application and review process are described in the next section (The EPPT Application and Review Procedures).

- Only the specimens from subjects who have signed the appropriate consent will be released.

- Once a study is approved, data will be released only as "restricted-use" datasets. No identifying information will be provided in the released data sets.

- Data are non-transferable unless prior authorization by NCI has been granted.

- Recipients of EPPT samples are required to sign and abide by a NCI Material Transfer Agreement (MTA).

- Sample processing (Sample aliquoting, microbiome extraction, QC sample insertion and batching) shall be done at the EPPT central processing laboratories, unless otherwise negotiated during the review and approval process.

- Laboratory analyses shall be conducted in a blinded fashion. The linking of laboratory data with the corresponding individual data shall only be performed by the EPPT coordinating center, and only after generation of the data. Analytic datasets will then be sent to the investigator who generated the data.

- Upon completion and publication of the study, laboratory data and final study results, with an accompanying data dictionary, shall be returned to the EPPT Trial by the investigator.

- EPPT Biospecimen Committee adopts general NIH policies on data sharing, with adaptation to ensure participant privacy consistent with the informed consent. Raw and processed data as well as datasets used in a published and completed study will be made available for other appropriate research after investigators have completed their study aims. Raw and processed data will ultimately be incorporated into the study tracking system and linked to the original study and to the samples. Investigators may also be contacted by other investigators wishing to collaborate prior to completion of their study aims.

- Investigators are encouraged to develop proposals with realistic scope and focused aims, achievable within a reasonable period of time.

- Investigators have up to three years from the proposal approval time to request the shipment of samples and commence activities on the study. Investigators are required to complete annual progress reports and expected to submit laboratory analysis results within 2 years after receipt of the samples. If an approved study remains inactive for three years, due to lack of funding or other issues, the

application will be considered withdrawn. A new application will need to be submitted and reviewed if the investigator wishes to conduct the study again.

4. EPPT Biospecimen Research

EPPT strives to adapt to the NCI Best Practices and to improve management practices to ensure quality control/quality assurance of the biospecimens.

Consistent with the goals for evidence-based best practices, EPPT will support limited pilot studies to assess quality of the EPPT specimens or suitability of certain assays (note that an EPPT biospecimen application is required for all pilot studies). Specifically, EPPT may consider the use of certain EPPT specimens (as specified in the Specimen Use Guidelines) to systematically evaluate the quality of the EPPT samples with regard to:

- Assay reproducibility
- Long-term intra-individual variation in analyte levels
- Effects of long-term storage on certain analytes or assays
- Effects of different sample processing methods on certain analytes or assays

5. EPPT Biospecimen Application and Review Procedures

A goal of the EPPT Biospecimen application and review process is to ensure fair, equitable access to EPPT resources based on scientific merit and NCI priorities. Preliminary applications for access to the EPPT biospecimens are accepted year-round. Upon receipt, proposals are reviewed for feasibility by EPPT Biospecimen Committee. The purpose of this initial review is to ensure sample availability and concordance with EPPT Biospecimen scientific objectives and priorities. Upon acceptance of the preliminary application, a final application may be submitted.

Final proposals are reviewed by the EPPT Biospecimen Committee Review Panel (see Section 7) for scientific merit. The EPPT Biospecimen Steering Committee (see Section 7) makes the final decisions based on the Panel review results and recommendations. Final decisions are communicated in writing to the applicants along with reviewers' written critiques.

Application materials and all other relevant EPPT Biospecimen documents are posted on the Cancer Data Access System (CDAS) website https://cdas.cancer.gov/. Information on the specimens is also available on that website.

6. EPPT Biospecimen Proposal Evaluation Criteria and Considerations

Due to the exhaustible nature of the biospecimens, stringent evaluation criteria apply to the selection of proposal applications. In addition to the overall scientific and technical merits, a research proposal must demonstrate the need and suitability to use EPPT specimens. Parsimonious use of the samples is a must. Additional programmatic and resource management considerations will also be used to evaluate and prioritize research projects.

The below sections describe in more detail some of the specific requirements that are of particular importance.

6.1. Scientific and Technical Merit

6.1.1. Overall Study Design

Study design must be consistent with study aims, including appropriate choice of study subjects, assays, statistical methods, study power, and must address potential confounders and biases. Because of the importance of assay operating characteristics in the laboratory being used for a study, pilot studies may be needed to address inter- and intra-batch variability and inter- and intra-person variability, with the intraclass correlation coefficient (ICC) being a key parameter in determining the adequacy of approach. For high-dimensional data, a plan for independent validation should be included. Since some of the EPPT samples have been stored for many years, potential analyte degradation needs to be considered. Multiplex assay approaches that minimize volume requirements are preferred.

Laboratory discovery of new biomarkers may be supported on a case-by-case basis. Additional criteria may include, but are not limited to:

- Public health needs
- No other suitable resources are available
- Overall excellence in study design and data analysis plan
- Use of proven, matured technologies

- Parsimonious use of samples

6.1.2. Statistical Methods

Applications should include an analytic plan and a statistical methods section. It is also recommended that a biostatistician be included as a co-investigator. They should also include a proposed sample size and provide the estimated statistical power for the analysis. For studies with a large number of analytes, statistical adjustment for multiple comparisons must be used.

6.2. EPPT Biospecimen Programmatic Considerations

6.2.1. Collaboration & Coordination

Investigators not familiar with the EPPT trial and the EPPT biospecimens resource are particularly encouraged to seek collaborations or feedback. Duplicate or highly similar efforts are not supported in general. Investigators with similar ideas and approaches are usually asked to develop a collaborative project.

Programmatic and logistic coordination may be beneficial when multiple studies are ongoing and addressing related scientific questions. Use of a common sample and data set facilitates direct comparison or integration of data across studies. In addition, it is often necessary to coordinate among multiple studies so that the samples can be aliquoted at once, minimizing freeze/thaw cycles and saving labor cost. These considerations were key points in becoming involved in large consortia efforts to enlarge sample size.

Developing the most effective approaches for sample management is an on-going process and may evolve rapidly. The EPPT Biospecimen Committee does consider requests on a case-by-case basis, with application of the above described principles.

6.2.2. Balancing Current & Future Needs

Management of the biologic sample resources requires judicious balancing of the need to further the NCI goals in the short-term *versus* preserving samples for unforeseen future uses. The EPPT leadership takes stewardship of the resource most seriously, and decision rules, documented in the EPPT Biospecimen Use Guidelines, have been established to assure maintenance of critical levels of the samples for future studies for all study subjects.

Demands for samples will certainly increase with advances in the science, but time may also work in our favor, with advanced technologies tending to require less and less sample. For example, the serum requirements for protein based multiplex assays have fallen over the years.

6.2.3. Quality Control

Certain quality control measures should be incorporated into proposed assays. Pilot studies will be required for new assays to establish assay reproducibility. A pilot study typically involves a small number of samples, with the assays done laboratory-blinded and in repeat samples. Data from a pilot study must be evaluated and approved by the EPPT Biospecimen Committee before full analytic samples can be released.

Systematic blinded QC sample insertion in the full analytic batch is necessary for monitoring assay quality. This is particularly important when samples are being assayed over an extended period of time. To minimize sample deterioration, thawing of samples will be coordinated to the extent possible at the EPPT processing lab. Aliquots of various sizes will be made at the first thawing of the samples to reduce freeze/thaw cycles.

6.2.4. Parsimonious use of samples

Regardless of study types, parsimonious use of the samples is a must, as EPPT samples are precious and depletable. To ensure that no amount of the biospecimens will be wasted, investigators must provide detailed justifications for the number of samples requested. Investigators may be asked to list the exact number of samples needed for each assay or laboratory method.

7. EPPT Biospecimen Management Infrastructure

The NCI Division of Cancer Prevention (DCP) oversees the management of the EPPT Biospecimen program. The Division is committed to supporting the EPPT Biospecimen infrastructure, providing extensive capabilities in biospecimens management and tracking, as well as scientific coordination, administration, and strategic planning.

7.1. EPPT Biospecimen Steering Committee

NCI guidance and oversight of the management of the EPPT Biospecimen is carried out by the EPPT Biospecimen Steering Committee (SC). The SC develops management policies and procedures, provides oversight and direction to the day-to-day management of the studies, and resolves conflicts over management and policy issues. The SC is composed of NCI staff from the Division of Cancer Prevention (DCP and will include the DCP Organ Group Chiefs. All decisions of the SC are subject to review and approval by the DCP EPPT Director.

7.2. EPPT Biospecimen Review Panel

The EPPT Biospecimen Review Panel is responsible for the peer-review of proposals submitted to the EPPT Biospecimen program. The panel is comprised of DCP scientists, biostatisticians and if needed, additional NCI *ad hoc* reviewers with specialized areas of expertise. The Panel makes recommendations to the EPPT Biospecimen Steering Committee based on scientific and technical merits of each proposal.

The Review Panel will be assigned per request by the EPPT Director. It will include DCP Consortia Medical Monitors and Scientific Leads and a statistician. Ad Hoc may be chosen for specialized areas of expertise. At a minimum, the Review Panel that is constituted for each received proposal will be composed of: 1) the Scientific Lead and/or Medical Monitor involved in the parent clinical trial, 2) two additional DCP scientific staff members who were not involved in the trial, and 3) a statistician. The panel will make recommendations based on scientific and technical merits of the proposal to the EPPT Director, who make the final decision regarding the proposal.

7.3. Contract Support

Contract support coordinates the EPPT Biospecimen application and review processes and monitors progress and tracks status of all approved studies. Contractor also provides support for day-to-day biospecimens management actives, and the post-approval sample requisition process.

7.4. Study Management and Tracking

The Cancer Data Access System (CDAS) is developed and maintained by a contractor. All completed and on-going studies are stored in the database, including proposal abstracts and annual progress status. Prospective investigators can search for past and

current research activities that may be related to proposed studies, thereby avoiding duplicate effort. The EPPT Biospecimen proposal review process is also managed and tracked by this database system.

7.5. Biospecimens Use Guidelines

A separate document entitled “Biospecimens Use Guidelines” has been developed to provide specific guidelines for each material type. The goal of the guidelines is to prevent sample depletion, and to ensure appropriate use of the samples, including quality controls. Sample selection must be based on the guidelines. Sample requests that violate the guidelines must be approved by the EPPT Biospecimen Committee.

8. EPPT Biospecimen Appeal Process

If an applicant has concerns about an EPPT Biospecimen Panel review and wishes to appeal the review outcome, he/she must submit a formal appeal letter within 30 days of the date on the final decision letter. An appeal letter must describe specific issues with the review. Appeals based solely on differences of scientific opinion will not be accepted. The EPPT Biospecimen Steering Committee will conduct the initial review of the appeal and make recommendations to the NCI DCP EPPT Director. The EPPT Director will make the final decision. There are three possible outcomes: 1) the appeal has merit and the application is approved, with or without certain conditions; 2) the appeal has merit and the application will be re-reviewed in the next round; and 3) the appeal has no merit and is rejected. The outcome of an appeal is final and cannot be appealed again.

9. EPPT Biospecimen Policy on Addenda

Certain circumstances may merit an addendum request to an approved on-going EPPT Biospecimen study. The addendum process is intended, in general, for small scale extension of an existing EPPT Biospecimen project. Requests of no more than 10% of the original request, either sample size or amount of the materials, are considered suitable for an addendum. Requests larger than 10% of the original approved requests, or limited expansion of scientific scope or aims, may be considered on a case-by-case basis by the EPPT Biospecimen Steering Committee. In general, no more than 3 addenda should be submitted per study (an addendum that does not involve new biospecimens, such as adding a PI or changing PI institution, is not counted toward the allowance).

Addenda that substantially expand the scope of the project—for example, examining a different class of markers, a different technology of assessment, or a different endpoint, will not be approved. These require a new application. The EPPT Biospecimen Steering Committee will make final decisions to accept or deny addendum requests.

10. EPPT Biospecimen Data Return and Data Sharing Policy

Laboratory-generated data on EPPT samples through an EPPT Biospecimen study must be returned to the EPPT database.

As described above, blinded samples are shipped to the investigator-designated laboratory. Investigators must submit the laboratory generated data and data dictionary to EPPT staff in order to receive an un-masked analytic dataset from which to perform their analysis.

Upon publication of the study, the raw laboratory generated data, a cleaned version of the data, final study results, and an accompanying data dictionary shall be returned to the EPPT Trial by the investigator.

Below is the list of data elements and other information that must be submitted to EPPT.

Assay data (Format: Excel or SAS)
For each sample provide the
following:

1. Sample ID (provided by EPPT)
2. Marker name(s) (include full protein name, gene symbol and aliases so that there is no ambiguity in the marker identity)
3. Marker measurement(s) (specify unit of measurement, assay batch number)
4. Name of the assay platform
5. Date and time assay performed
6. Reagent lot/batch number
7. Operator(s)
8. Instrument(s) and calibration
9. Any QC data on the EPPT samples (as an example, PH level)
10. All other QC data
11. Missing value indicator and reason(s) for the missing value
12. If applicable, case/control predictions

Descriptive information

1. Name of the laboratory that performed the assay measurements
2. Name of the Principal Investigator responsible for the data submitted/Owner of the data
3. Study ID (EPPTB-XXXX-XXXXX) and title
4. Technical description of the assay platform(s)
5. Detailed assay protocol, including specimen preparation method
6. Description of method for normalization of marker measurements if applicable

Decision rule for classifying samples (if applicable)

1. Name of a point-of-contact for the classification rule submitted
2. Detailed description of the classification rule for classifying subjects as cases or controls. If the classification rule is based on a propensity score, provide a detailed technical description of how that score is determined.

These laboratory data will be made available to other investigators who request them after the data have been published. Investigators may request published study data online via the Cancer Data Access System (CDAS) (https://cdas.cancer.gov/). Prior to releasing published study data to other investigators, The EPPT Biospecimen Committee will contact the original study investigator (s) to confirm that the data are indeed published and that the proposed research does not overlap with an in progress research aim that was previously approved by EPPT.