National Cancer Institute

Pancreatic Cancer Detection Consortium (PCDC)

Manual of Operating Procedures

Working Document

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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OVERARCHING PRINCIPLES

The Manual of Operating Procedures (MOP) is intended to capture some of the organizational and operational elements of the Pancreatic Cancer Detection Consortium (PCDC). It is not intended to replace or interpret the National Institutes of Health (NIH)/National Cancer Institute (NCI) Policies, Funding Opportunity Announcement (FOA; PAR-15-289), and/or Terms and Conditions of Award that govern the varied sets of activities to be conducted under this cooperative agreement. All entities and individual researchers and/or research staff that are directly or indirectly funded by the PCDC are expected to abide by the terms and conditions of award, including NIH/NCI Policies and the FOA (https://grants.nih.gov/grants/guide/pa-files/PAR-15-289.html). In the event of a discrepancy, NIH Policies/FOA/Cooperative Agreement Terms and Conditions of Award supersede institutional policies, the MOP, and researcher's and/or research staff's opinions.

SECTION 1: PCDC ORGANIZATION

Overview

The Division of Cancer Prevention, NCI, created the PCDC to support investigator-initiated, collaborative research to develop and test new molecular and imaging biomarkers to improve the detection of early stage pancreatic ductal adenocarcinoma (PDAC) and its precursor lesions and to identify individuals who are at high risk of developing PDAC and are candidates for early intervention. Details about the consortium goals and structure are outlined in Section I - Funding Opportunity Description in the FOA: PAR-15-289.

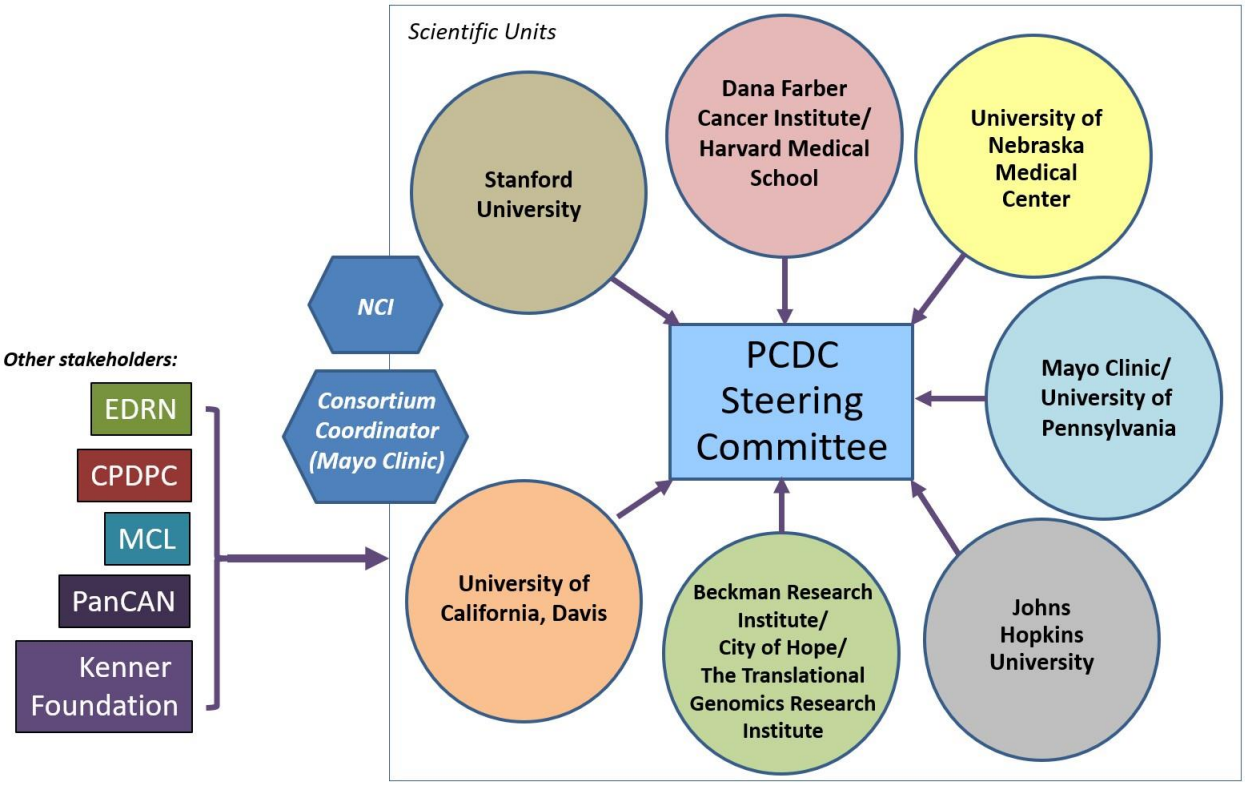

Figure 1 . Organizational structure of PCDC. The U01 Scientific Units form the consortium and is governed by a Steering Committee. PCDC Units interact with other existing NCI Programs and stakeholders such as the Early Detection Research Network (EDRN), Consortium for Molecular and Cellular Characterization of Screen-Detected Lesions (MCL) and the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC), and Foundations such as the Kenner Family Research Fund (Kenner Foundation) and the Pancreatic Cancer Action Network (PanCAN).

PCDC Units

The PCDC has two scientific components:

- ***The PCDC U01 Research Units***: The PCDC Research Units are responsible for conducting research to develop and test biomarkers and imaging methods for improved detection of early stage PDAC and its precursor lesions and for the collection of longitudinal samples (e.g., tissue, cystic fluid, serum, plasma) and other significant specimens for the non-invasive development of biomarkers. For each Research Unit, a description of the project and available resources for sharing are provided on the PCDC website (https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection-consortium).
- ***The Consortium Coordinator (CC)***: The CC is responsible for coordination of consortium-wide meetings and conferences and collaborative activities, and for data management and protocol development for the biorepository (see Section 3 for details).

SECTION 2: STEERING COMMITTEE

2.1 Steering Committee Overview

All scientific Units of the consortium are linked through a governing body, the Steering Committee. The Steering Committee (SC) includes representatives of the PCDC Research Units (PDs/PIs of the U01 awards), the CC, and an NCI Project Coordinator. In addition, Chairs of

other NIH programs may serve on the Steering Committee as ex officio members. The responsibilities of the SC are to manage, oversee and coordinate the integration of efforts among the awardees and all collaborative activities, including the development of uniform standards for specimen and data collections and analysis. It also includes overseeing research prioritization, research community outreach, information flow optimization, and facilitation of resource development and sharing. Details on the structure of the activities/responsibilities of the SC are provided in the FOA (Section VI. 2. Cooperative Agreement Terms and Conditions of PAR-15-289).

According to the requirements of the Cooperative Agreement, the SC meets as necessary to conduct the business of the PCDC, typically, once a month via WebEx. Additionally, a face-to-face SC business meeting is held each year that the PCDC members are expected to attend; additional meetings are scheduled as needed. The time and site for these meetings are determined by the SC members and NCI Program Directors. Principal Investigator(s) from each Cooperative Agreement are required to attend the in-person SC meeting each year. If unable to attend at least one qualified representative (the PI, Multi-PI or Co-Investigator) from each Cooperative Agreement should attend the SC meeting. The minutes of the SC meetings are prepared by the CC and distributed to the members of the SC for approval at the next SC meeting.

2.2 Voting Members of Steering Committee.

While investigators who comprise PCDC units may take part in conference calls and meetings of the SC, the qualified representatives (one per U01and typically the contact PI of each grant) and the NCI Program Coordinator will serve as voting members of the Steering Committee. In the event that the PI cannot be present, the MPI or a designated proxy may vote for the PI.

2.3 Steering Committee Responsibilities

Primary responsibilities of the Steering Committee include, but are not limited to, the following activities:

- Establishing consortium policies and procedures;
- Establishing policies and procedures for collaborative projects, protocols, and consortium-defined projects;
- Develop guidelines for the collection and distribution of specimen reference sets for collaborative research;
- Setting the overall research priorities for the consortium and identifying emerging research opportunities which can be best explored through a joint collaborative effort via the Consortium;
- Serve as a nucleus for a broader outreach, on behalf of the PCDC, to the entire extramural research community.

2.4 Chairmanship or Co-Chairmanship

NCI consortia generally have a Chair and Co-Chair or two Co-Chairs, per decision of the SC. Any member of the SC can offer nominations for the Chair or Co-Chair. The term of office for the Chair, or Co-Chair, is five years - the entire period of the funding cycle. The Chair, or Co-Chairs, makes all appointments for Chairs of Subcommittees and Working Groups in consultation with the SC. The Chair, or Co-Chairs, serve at the pleasure of the full SC and NCI and is subject to removal as Chair, or Co-Chair, at any time.

PCDC has two Co-Chairs, selected by the SC. While it is expected that the Co-Chairs will serve in their capacity for five years, there may be instances whereby the Chair, or Co-Chair, may be unable to continue either due to their own personal circumstances or by decision of the PCDC SC. When possible and under these circumstances, it is preferred that there is an overlap of at least 6 months between the incoming and outgoing Chair in order to ensure a seamless transition.

2.5 Duties of the Co-Chairs

Primary responsibilities of the SC Co-Chairs include, but are not limited to, the following activities:

- Preside at all meetings of the SC;
- Appoint the Chair (and Co-Chair, if necessary) of Subcommittees and Working Groups;
- Invite consultants as needed to Subcommittees and Working Groups;
- Appoint PCDC liaison members to other organizations when invited to do so;
- Serve as an ex-officio member of Subcommittees and Working Groups.

2.6 Quorum

For holding meetings, including conference calls, a quorum is defined as the presence of SC voting members from at least 50% of the PCDC sites and the NCI-designated Project Coordinator or another NCI Program representative. If a quorum is not present, the meeting or conference call can be cancelled. In the absence of a quorum, questions or proposals cannot be decided by vote by the SC.

SECTION 3: CONSORTIUM COORDINATOR

3.1 Overview

The Consortium Coordinator is responsible for coordination of consortium-wide meetings, conferences and collaborative activities, and for data management and protocol development for the biorepository.

3.2 Consortium Coordinator Responsibilities

The PCDC team at the Mayo Clinic are responsible for the consortium coordination functions. These activities include:

- Providing logistical and administrative assistance in arranging meetings to allow for efficient interactions, consultations, and oversight functions of the Steering Committee (e.g., preparing, distributing and maintaining minutes);
- Working with NCI Program Staff to develop and maintain an interactive webpage to publicize the activities of the Consortium, to announce the availability of Consortium-supported resources and receive input from investigators (https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection-consortium); Developing and maintaining a researcher contact list, Consortium documents including Manual of Operations and SOPs, standard procedures/protocols for data and specimen collection;

- Working with NCI Program Staff to structure and populate with PCDC documents, publications and resource materials on a password protected shared portal (https://ncihub.org/);
- Supporting the development, coordination, implementation, and conduct of Consortium collaborative research protocols and monitoring protocol adherence, data collection and submission;
- Creating and managing a patient registry with virtual biorepository that will encompass clinical and demographic information as well as available biospecimens at participating sites;
- Supporting the formation and distribution of Consortium biospecimen sets, biospecimen tracking and analyzing data that result from the use of these specimens;
- Creating and managing infrastructure for data management, bioinformatics, clinical data, and other requirements to support the Consortium Units.

SECTION 4: SUBCOMMITTEES

4.1 Overview

Subcommittees are responsible for developing policies and guidelines as directed by the PCDC SC. Subcommittees report directly to the PCDC SC Co-Chairs; and their activities and recommendations are subject to review and approval by the PCDC SC. Subcommittees may, at the discretion of the SC, be created or dissolved as needed. Subcommittees are led by a Chair, who may be PCDC Principal Investigators or co-Investigators. The term of office for the Chair is one year with eligibility for re-election by Subcommittee voting members. Voting members of the Subcommittees are PCDC Principal Investigators.

Subcommittees meet once a year in conjunction with the SC business meetings. Conference calls are made any time on the recommendation of the Co-Chairs of the SC or the Chair of the individual Subcommittee.

4.2 Data Manager Subcommittee

4.2.1. Objective

The objective of the Data Manager Subcommittee is to establish the rationale and conditions for sharing technology, data and other resources among investigators within and external to the PCDC. Other objectives of the Subcommittee are to establish guidelines for the PCDC data structure and common data elements (CDEs), and to provide a forum for biostatisticians/analysts within PCDC to collaborate on research pertinent to PCDC.

The Data Manager Subcommittee is chaired by the Lead Statistician of the CC. The Lead Statistician is responsible for reporting back to the PCDC SC on a routine basis and obtaining the necessary approvals from the PCDC SC prior to implementing any data management decisions. The Data Manager Subcommittee meets on a quarterly basis and consists of up to two representatives (Statisticians, Project Managers, etc.) from each U01 site.

4.2.2. Responsibilities

- Develop guidelines, as needed, for sharing resources within and outside the PCDC;
- Develop guidelines for coordinating prioritized projects across the Consortium;

- Develop PCDC data and metadata standards, including common core, project-specific and work group-specific CDEs;
- Develop guidelines for security levels of the centralized data system;
- Develop guidelines for internal and external data sharing that include mechanisms to ensure that the data are used appropriately;
- Develop guidelines for and assist with data set integration, pooling and access across the PCDC and with other NCI programs;
- Monitor the quality of signature data captured;
- Develop guidelines for posting materials on the PCDC website;
- Review patient privacy requirements for PCDC;
- Designated representatives from each U01 site attend Steering Committee calls.

SECTION 5: WORKING GROUPS

5.1 Overview

Working groups are established by the PCDC SC, for a finite period of time, to address specific scientific, technological and resource questions that are relevant to multiple sites and are in line with the goals and mission of the PCDC. Working Groups are led by a Chair and a Co-Chair, who may be PCDC Principal Investigators or co-Investigators. The leadership of each Working Group must be approved by the PCDC SC. The term of office for the Chair and Co-chair is one year with eligibility for re-election. Membership on a Working Group is by self-selection among the members of the PCDC Units and the NCI Program Directors. Working Groups meet monthly via teleconferencing and once a year in person during the annual face-to-face SC meetings. The Chair and Co-chair set the agenda for each conference call and in-person meeting and moderate the meetings. The CC captures and maintains minutes from all meetings of the Working Groups and these are posted in a secure area of the PCDC website.

5.2 Methodology

The objectives of the PCDC Methodology Working Group are to:

- Develop new biostatistical and bioinformatics approaches that are relevant to the conduct of studies to
    - Identify discriminatory biological determinants (driver genes, pathways, tumor cell-microenvironment interactions, etc) among screen detected cancers,
    - Develop biomarkers for distinguishing aggressive from indolent lesions, and
    - Establish the reliability and interpretation of findings.

5.3 PCDC Signature Protocols

A key strategy for PCDC to effectively advance early detection research in pancreatic cancer is to identify and build longitudinal high risk cohorts. This would involve prospective collection and maintenance of data from baseline to followup, and biobanking of repeated non-invasive biospecimen collections (e.g., blood, saliva, stool, urine). The research to be performed would compare samples of participants who develop cancer over time compared to those who do not. Tests that would be applied to the biospecimen collections would use subsets of participants in designs that would provide the maximum amount of information about the performance of the assays in predicting who has cancer at an early stage. The maintenance of protocols will be

maintained by the PCDC Administrative Core. The cohorts will require a long-term investment and will be most successful with multiple contributing sites. Detailed protocols suitable for local IRB approvals are attached in the Appendix to this Manual.

5.3.1. Signature Cyst Fluid Collection Protocol

The collection of biosamples and data for patients with pancreatic cystic neoplasms into a registry in the PCDC will develop a longitudinal cohort of high risk individuals. The vast majority of these individuals will harbor pre-malignant cystic lesions, of which a subset over time will transform into pancreas cancer. These high risk individuals will be recruited at each site, and biospecimens will be logged, stored, and administered, and studied by consensus protocols of members of the PCDC. Relevant clinical, demographic characteristics of the individuals will be recorded along with imaging characteristics of the cystic neoplasms.

5.3.2. Signature Family Study Protocol

The collection of biosamples and data for the family-based recruitment into a resource/registry in the PCDC will develop into a longitudinal cohort of individuals and family members currently without pancreatic cancer, but who are at high risk due to family history of pancreatic cancer or predisposition gene mutation status. High risk individuals will be recruited at each site, and biospecimens will be logged, stored, administered, and studied by consensus protocols of members of the PCDC. Inclusion of genetic status of high risk individuals would add great value to the cohort.

SECTION 6: POLICIES AND PROCEDURES

6.1 Set-Aside Funds

Set-Aside Funds ($100,000 Direct Cost per year per Unit) are funds dedicated for collaborative studies developed within the PCDC. Collaborations between PCDC members and/or between PCDC members and outside non-PCDC parties are permissible. This structure is intended to provide a novel and essential venue to facilitate interdisciplinary collaborations and progress, and to make information on molecular and cellular characteristics of early lesions accessible to the broader research community.

Collaborative studies must be submitted as a team and budgeted using the Set-Aside Funds for the parent PCDC Cooperative Agreement award. Funding for multiple years will be allowed subject to annual approval and to verifiable sufficient progress. The use of Set-Aside Funds will be restricted to collaborative projects relevant to the consortium’s objectives, and must be reviewed and approved by the PCDC SC and other NCI members.

6.1.1 Release and Use of Set-Aside Funds

A Principal Investigator may only apply for the Set-Aside Funds within his/her Cooperative Agreement award. Set-Aside Funds may only be used for projects that complement the scope of the Cooperative Agreement award; and abide by the terms and conditions section of the parent U01 grant award. More than one investigator may request the release of Set-Aside Funds to be pooled for one, multi-site collaborative project. A Principal Investigator may apply for more than one year’s Set-Aside Funds by proposing a multi-year collaborative project; however, an annual status report must be submitted to NCI and should detail how the Set-Aside Funds were used

before subsequent year funds are considered for release. The status report may be submitted as part of the U01 award annual progress report (Type 5/RPPR) submitted by the Principal Investigator. The applications for the release of Set-Aside Funds are reviewed by the SC at the monthly SC calls. Applicants must apply for release of the Set-Aside Funds within 60 days of the anniversary date of their Type 5 application. If you are entering the 2nd year or beyond in a multi-year set-aside study, please contact your Program Officer prior to submitting your previous year's progress report. The timing of submitting the progress report will help to ensure that your set-aside funding for the next year of the study is not interrupted.

6.1.2 Application Requirements for Release of Set-Aside Funds

The proposal for use of Set-Aside Funds must follow the NIH Format, as used in PHS Form 398 (Set-Aside Funds Application). The budget cannot exceed the allocated set-aside funds for the project.

The Research Plan Section of the application cannot exceed 6 pages. Electronic copies of the proposal, signed by an Authorized Institutional Official, should be submitted to the NCI Program Directors assigned to the PCDC U01 grants involved in the collaborative project.

A brief description of the scope of the proposed collaborative project as it relates to the parent grant(s) should be provided. This includes a brief summary of the activities that were included in the parent grant and which encompass those in the proposed collaborative study. This section should provide a description of the proposed collaboration including research design/proposed scientific activities and methods and data analysis. The relationship of the Set-Aside request to the parent grant should be described. For the proposed research project, include the following:

- Specific aims, Background, and Significance.
- Description of how the outcome of the proposed study will provide additional value to the underlying research (parent grant) of the PI and the collaborating investigators.
- Preliminary studies.
- Experimental design presented in adequate detail to allow scientific evaluation of the feasibility.

NB: Set-Aside Project concepts and the respective aims can be brought to the PCDC SC in advance of turning in a full application to obtain any feedback that could aid in positive funding outcome.

6.1.3 Review Criteria

PCDC Principal Investigators are encouraged to consider basic, mechanistic, and/or biomarker identification/validation-based applications for collaborative projects using the Set-Aside Funds. Considerations to disparate scientific disciplines with relevance to pancreatic cancer and within the scope of the PCDC consortium are also encouraged.

The collaborative research project must be within the general scope of the Principal Investigator's active PCDC-funded grant and cannot be duplicative of any active or previously funded research topic for any of the consortium members.

Review criteria for release of Set-Aside Funds are based on the parameters outlined in PAR-15-289. Selection factors and priorities include, but are not limited to, the following:

- The importance of the specific questions to be asked; the potential scientific impact of the proposed collaboration and its relevance to the overarching mission of the PCDC;
- The application must clearly state the need for such a collaboration (unique expertise, infrastructure, resources) and provide plans for the collaborative activity(ies);
- The novelty or uniqueness of the collaboration, and the need for said collaboration to address unmet needs of the PCDC;
- The expertise of the proposed research/scientific team to conduct and achieve the goals of the collaborative study or accelerate the pace of scientific research.

roposed activities should also:

- Demonstrate sound study/experimental design;
- Provide a realistic scope of work, given the time and budget requested;
- Clearly document the contributions of each of the participating collaborative units and individual researchers. Applicants must demonstrate adequate plans for effective interaction and coordination with PCDC components, such as the SC, the CC, or the NCI;
- Investigators and entities they represent must state their willingness to collaborate and share information;
- In case of genomic and proteomic profile studies, investigators will be required to abide by the NIH data sharing guidelines.

A project does not have to be strong in all review categories to be considered highly meritorious. For example, a methodology or infrastructure-related application may not be judged to be at a high level of scientific merit yet it may be a critical component in an overall plan to achieve PCDC goals and may represent a high level of cooperation and interaction among investigators toward PCDC objectives.

It is preferred that progress reports for Set-Aside proposals be included in the parent grant RPPR. However, the three options for providing progress reports on the set-aside project is via the RPPR, during submission of carry-forward request or by request of the NCI Program Officer prior to the release of funds.

6.2 Site Visits

Each PCDC Unit should be site visited by a panel comprised of external consultants or the NCI Program staff and other experts on an “as needed” basis. The site visit should be brief (preferably half a day or less) but enable a thorough review of the scientific progress, future scientific plans, performance metrics (e.g., publications, collaborations, resources for PCDC), facilities and staff in support of the PCDC charge. The site Principal Investigator(s) should provide a 2□3 hour presentation to review scientific progress, describe new and ongoing scientific initiatives for PCDC, and demonstrate productivity. The Principal Investigator(s) are encouraged to share problems, concerns, and questions to the site visit team so that the process is interactive and collegial. While an agenda and presentation will be necessary, no scoring will be used for evaluation of the Unit.

6.2.1 Frequency of Site Visits

The frequency of the site visits will be determined by the NCI. However, it is anticipated that one initial site visit by NCI Program Officers will occur in year one, if possible, and one mid-grant site visit (for a five-year grant cycle) will occur between year 2 and year 3. Additional site visits may be required when deemed necessary by the NCI.

Deficient performance and remedies will be conducted in accordance with HHS 45 CFR, Part 74 and other pertinent regulations.

SECTION 7: PCDC INFORMATION SHARING

7.1 PCDC Public Portal

The principal focus of the PCDC Public Portal (https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection-consortium) is to raise the awareness of the public about PCDC. It provides an online mechanism to distribute information and results from the PCDC to the public, including news, announcements of opportunities, availability of online data sets, information about PCDC studies, access to various PCDC resources, and overall information about the PCDC program. The Public Portal also serves as a gateway to other PCDC tools and databases. It provides publishing capability so that new information can be easily reviewed and published to the portal.

7.2 PCDC Secure Web Portal

The Consortium Coordinator (CC) works closely with the NCI to develop and maintain a PCDC Portal (https://ncihub.org/). The Portal, with both public and secure access divisions, will contain general PCDC information, such as contact information for all participating institutions, committee and subcommittee membership, upcoming events, etc., as well as items that are less public, such as data from collaborative studies, approved validation proposals, manuscript drafts, etc. Due to the sensitive nature of some of the information available through the PCDC Portal, only individuals approved by the CC and/or NCI PCDC Program Officers will be given access to the secure division of the PCDC Portal. Access to the secure division of the PCDC Portal will require a log-in ID and password distributed by the PCDC CC.

SECTION 8: PCDC INFORMATICS AND DATA MANAGEMENT

The Consortium Coordinator (CC) will provide oversight of all resource databases shared in common across the PCDC, and will facilitate data sharing when papers emanating from the PCDC are published. A central database that contains subject-level data will contain prospectively accrued study subjects using Common Data Elements described below. The purpose of the databases are to facilitate reporting and future planning of studies that would utilize the data or biospecimens.

8.1 Aggregate Accrual Reports

The PCDC biostatisticians will collect and report aggregate accrual summaries to the Steering Committee. The report will consist of participant accruals by PCDC site and stratified by diagnosis.

8.2 Centralized Database: Common Data Elements

The PCDC Common Data Elements (CDEs) have three main components:

- wording of the questions used to collect data,
- possible responses to the questions,
- the data format for sharing and/or transmission of the data within PCDC.

The CDEs will help standardize data that is collected and stored at all sites to ensure consistency in data and specimen sharing. They will also facilitate meaningful mapping of previously captured data to PCDC standards. Any PCDC site collecting new prospective data for PCDC studies are required to use the PCDC CDE.

Currently, CDEs have been developed by the PCDC for prospective specimen collections. These CDEs capture patient-level data from the Baseline and Follow-up Core CDEs which are comprised of a participant ID, protocol ID, site ID and basic epidemiologic data relevant to PCDC. Specimen level data captured via the CDEs, includes information regarding the sample type and pre-collection treatment as well as on the processing and storing of the specimens that were collected. The CDEs have been further extended to capture information on participants who contribute biospecimens to the PCDC Signature Protocols described in Section 5.3.