Early Detection Research Network

Manual of Operations

Version 5.0

Revision History

Version	Date	Change
1	01-11-01	Created Sections 1, 2, 3, 4, 5, 6 and Appendices I, II, III
1.1	07-19-01	Created Appendix IV
	10-01-01	Created Revision History page; Edited Sections 6.2.6 and 6.2.7
1.2	05-02-02	Revised Sections 2.2.1, 3.1, 3.1.1, 4.1, and updated Appendices II and III
	02-24-03	Revised Section 6.1
	02-25-03	Revised Appendix III
	01-05-04	Revised Appendix III
1.3	09-16-2004	Incorporated various edits deemed necessary by NCI and the DMCC
	09-16-2004	Incorporated Appendix IV into body of manual (Section 7)
	09-16-2004	Removed Appendices I, II, and III
	9-16-2004	Created new Appendix – Website Users Guide
2.0	10-28-2004	Draft Document
2.1	2-23-2005	Revised Sections 1-6
3.0	03-03-2005	Final
4.0	03-01-2011	Revised to reflect changes in the 2010-2015 funding cycle
5.0	09-28-2016	Revised to reflect changes in the 2016-2021 funding cycle

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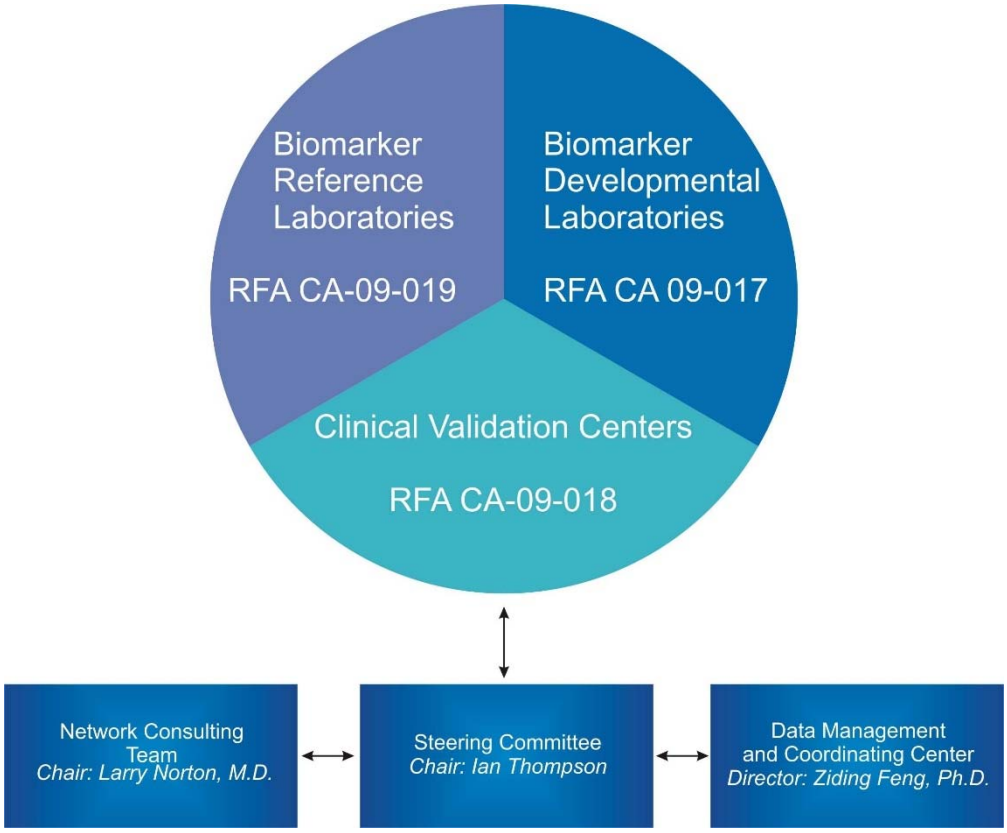
SECTION 1 ORGANIZATION AND DEVELOPMENT

The Division of Cancer Prevention in the National Cancer Institute created the Early Detection Research Network (EDRN) to support investigator-initiated, collaborative research on molecular, genetic and other biomarkers for cancer detection, risk assessment, prognosis and diagnosis. A number of programmatic review groups at NCI recommended that the EDRN be created and continued.



Funded separately through peer-reviewed Cooperative Agreements, the EDRN has four components:

- Biomarker Developmental Laboratories (BDLs): The BDLs are responsible for the development and characterization of new or refinement of existing biomarkers. BDLs may be multi-PI.
- Biomarker Reference Laboratories (BRLs): The BRLs serve as a Network resource for clinical and laboratory validation of biomarkers that include technological development, refinement and quality control. BRLs are expected to work with EDRN BDLs and CVCs.
- Clinical Validation Centers (CVCs):. The CVCs conduct clinical research on the validation of biomarkers and participate in Network-wide clinical validation of biomarkers.
- Data Management and Coordinating Center (DMCC): The DMCC supports statistical and computational analysis and informatics infrastructure, coordinates network-wide meetings and conferences and serves as the Coordinating Center for validation studies.

The network is governed by the Steering Committee, consisting of the Principal Investigators of the EDRN and NCI staff. The Network also has a Network Consulting Team composed of non-EDRN investigators appointed by EDRN Steering Committee to review the progress of the Network and to recommend new research opportunities.

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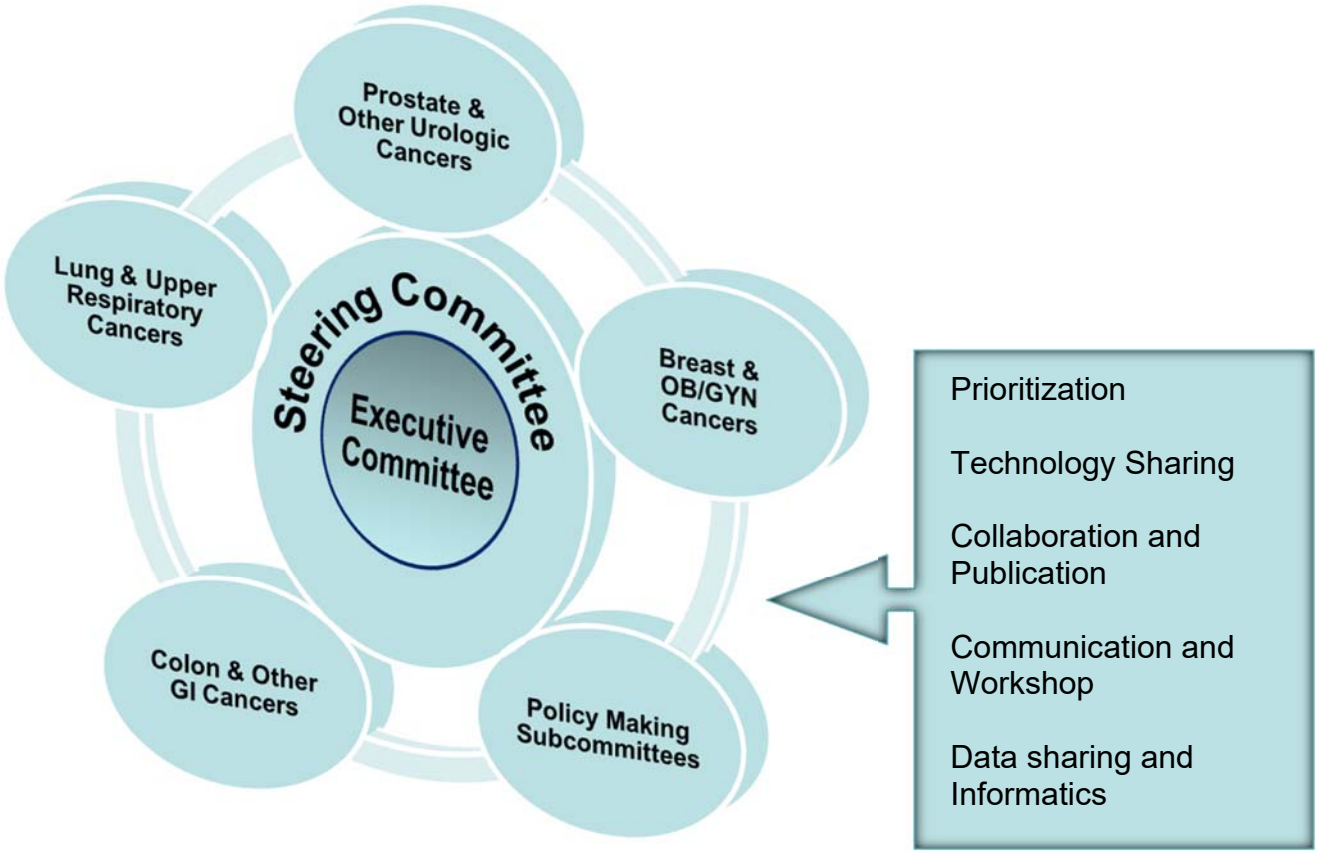
These procedures provide guidance for the administrative and operational activities of the EDRN and may be modified or revised by approval of the Steering Committee as experience and need dictates. Any member in good standing (i.e., a member who attends at least one Steering Committee meeting per year) may propose amendments to the EDRN Manual of Operations.

1.1 Statement of Objectives

- To support and facilitate a broad spectrum of research activities that address early development and initial validation stages of molecular biology and genetics, including biomarkers that can be applied in cancer risk prediction, early detection, primary prevention of cancer and diagnosis.
- To coordinate national and international research programs for the development of clinically useful biomarkers in preneoplastic lesions that accurately predict the risk of invasive cancer or the presence of early cancer in asymptomatic individuals not previously diagnosed with the disease.
- To support the development of databases on the utility of biomarkers and expression patterns that will serve as background information for larger validation and efficacy studies.
- To promote collaboration and communication with other programs at the NCI, other Institutes within NIH, organizations with the National Cancer Program, and academic and industrial leaders from relevant disciplines.

SECTION 2 COMMITTEES



2.1 Steering Committee

2.1.1. Overview

The Steering Committee (SC) has major scientific management oversight and responsibility for developing and implementing a collaborative Network research program including protocols, publications, and design. The Committee consists of a Chair, Co-Chair, the EDRN Principal Investigators or a designee, and the NCI Program Coordinator or a designee. A Principal Investigator cannot designate an Associate Member to replace him/her at an SC meeting. Members of the SC review all data collected in Network studies, monitor study results, follow-up, and report to the full SC upon request of the Chair. Each member has one vote.

According to the requirements of the Cooperative Agreement, there are 2 SC business meetings per year and one scientific workshop each 18 months that EDRN members should attend; additional meetings may be called as needed. The time and site for these meetings are determined by SC members. The Principal Investigator(s) from each Cooperative Agreement are required to attend at least one SC meeting each year. However, there must be at least one representative from each Cooperative Agreement, at every SC meeting. The minutes of the SC meetings are prepared by the DMCC as a matter of record and distributed to the members of the SC for approval at the next

meeting. NCI reserves the right to terminate a grant for failure to attend or have representation at SC meetings.

The PIs of a U01/U24 will serve as a voting members of the Steering Committee and will attend the Orientation meeting and two Steering Committee meetings in the first year and in subsequent years attend two Steering Committee meetings and an EDRN-Sponsored Gordon Conference or an EDRN-sponsored workshop every 18 months. The attendance of PI(s) at these meetings is considered an essential part of the grant.

Applicants must budget for travel and per diem expenses for SC meetings. In the first year, applicants should plan for two investigators, the principal investigator and an additional senior investigator, to attend a Planning Meeting and two SC meetings. In the second and subsequent years, applicants should plan for the PI and another investigator to attend two SC meetings and one workshop every 18 months.

The EDRN Steering Committee is comprised of EDRN Principal Investigators and NCI Program Coordinator. Exceptions to this membership can be brought to the Steering Committee for approval. Such exceptions may include the nomination of PI, funded by the NCI through another peer-review mechanism, for which the NCI has determined his/her inclusion to be of significant EDRN programmatic interest.

2.1.2. Responsibilities and Privileges

- Develop guidelines for operating the EDRN
- Coordinate the research program within the EDRN
- Develop criteria for reviewing progress of the EDRN
- Establish and track milestones
- Develop and implement rules for sharing data and resources
- Disseminate information on the availability of resources (tissues, new technologies, and patients) within the EDRN
- Develop criteria for selecting an Associate Member of the EDRN
- Develop criteria on the use of the Core Funds
- Develop and approve protocols for clinical research through the EDRN
- Develop criteria on evaluating and reviewing data on potentially promising new biomarkers
- Prepare annual Progress Reports for submission to NCI at the end of each fiscal year

2.1.3. Chair

The Chair and Co-Chair are elected by the full SC. Any member of the SC can offer nominations for the Chair and Co-Chair. The term of office for the Chair is five years with eligibility for re-election for one additional term (for a total of 10 yrs). The term of office for the Co-Chair is 2.5 years with eligibility for re-election for one additional term (for a total of 5 yrs). The Chair makes all appointments in consultation with the SC.

2.1.4. Duties of the Chair

- Preside at all meetings of the full SC
- Appoint and re-appoint members of Subcommittees, Review Groups, and designate special assignments
- Appoint the Chairs and Co-Chairs of Subcommittees, Review Groups, and Collaborative Groups
- Appoint ad-hoc committees as needed
- Invite consultants as needed to Subcommittees, etc.
- Appoint EDRN liaison members to other organizations
- Serve as a Co-Chair of the Executive Committee
- Serves as an ex-officio member of all Subcommittees, ad hoc Committees, and Task Forces
- Submit annual EDRN Progress Reports to NCI and the Network Consulting Committee
- Prepare the agenda for the SC meetings

2.1.5. Duties of the Co-Chair

- Serve as acting Chair during absence of the Chair
- Serve as chair of the Executive Committee

2.1.6. Quorum

For holding meetings, including conference calls, a quorum is defined as the presence of the majority of SC members. If a quorum is not present, the meeting will be cancelled.

2.2 Executive Committee

2.2.1. Overview

The Executive Committee (EC) consists of a Chair, Chair of the SC, Chairs of Collaborative Groups, at least one Principal Investigator from a BDL, BRL, CVC, and DMCC (if not represented in the Collaborative Group Chairs), and the NCI Program Coordinator or a designee. The Committee is chaired by the Co-chair of the SC. The term of office for the Chair is 2.5 years with eligibility for re-election for one additional term (for a total of 5 yrs). The EC meets as necessary to conduct the business of the EDRN, typically once a month on a conference call, or at the discretion of the Chair of the EC or SC. The minutes of the EC are prepared by the DMCC as a matter of record and distributed to the members of the EC for approval at the next meeting.

The Committee expedites the work of the SC and assists the Chair of the SC. It coordinates the administrative and research activities of the EDRN on a regular basis and provides a mechanism for communication on the management of the EDRN. The Committee makes recommendations on major policy issues to the SC.

2.2.2. Responsibilities and Privileges

- Facilitate the work of the SC and assist the Chair of the SC
- Coordinate the administrative and research activities of the EDRN on a regular basis and serve as a forum for communication on the management of EDRN
- Conduct routine business to consider distribution of funds and to review and recommend for approval all research proposals submitted to the SC
- Approve Associate Members
- Recommend the release of Restricted and Core Funds to NCI
- Act for the SC on administrative and scientific matters between the semiannual SC meetings
- Oversee responsibilities of the Collaborative Groups

2.2.3. Duties of the Chair

- Serve as Co-Chair of the SC
- Preside over meetings of the EC

- Prepare the agenda for EC meetings

2.2.4. Duties of the Co-Chair

- Serve as acting Chair during absence of the Chair
- Serve as chair of the Steering Committee

2.2.5. Quorum

For holding meetings, including conference calls, a quorum is defined as the presence of the majority of EC members. If a quorum is not present, the meeting or conference call will be cancelled.

2.3 Network Consulting Team

2.3.1. Overview

The Network Consulting Team (NCT) an ad-hoc group of extramural scientists, is independent of the programmatic oversight provided by the NCI who are appointed by the Director of the Division of Cancer Prevention, NCI. The NCT is a non-voting committee, composed of non-federal scientists, clinicians, patient advocates, and ethicists who are devoid of financial and/or collaborative affiliation with EDRN where a conflict of interest exists or may be apparent. At the recommendation of the Chair, EDRN SC ,ad-hoc consultants may be recommended to serve on the NCT. Ad hoc consultants may be called upon for consultation in areas where specific expertise is needed yet lacking in the NCT. Ad hoc consultants may be federal or non-federal scientists, clinicians, patient advocates, and ethicists.

2.3.2. Responsibilities and Privileges

The primary role of the NCT is to assist the EDRN in evaluating the overall Network concept. The NCT will assist in the evaluation and operation of the EDRN by:

- Exchanging facts, materials, or information pertaining to the review of progress and planning of research within the EDRN
- Providing non-binding advice of individual members (not consensus advice or consensus recommendations) to the EDRN SC or EC, when appropriate
- Reviewing the progress of the EDRN, which may include a member's participation in site visits
- Considering new research initiatives to ensure the EDRN is responsive to promising opportunities in early cancer detection research and risk assessment
- Serving as members on ad-hoc committees of the EDRN, including Review Groups, Working Groups and Collaborative Groups, and as Consultants to Subcommittees
- Assisting the EDRN SC in planning and organizing workshops and symposia
- Participating in EDRN workshops and symposia

- Serving as a liaison between the cancer research community and the EDRN
- Meeting with NCI and EDRN leadership at the request of the Chair, NCT, NCI, or Chair, EDRN SC

2.3.3. Chair

Appointed by the Director of the Division of Cancer Prevention, NCI for an initial 5-year term and is renewable for an additional 5-year term.

2.3.4. Duties of the Chair

- Presides over all meetings of the full NCT
- Serves as liaison with the NCI Program Coordinator or designee and the Director of the Division of Cancer Prevention, NCI

SECTION 3 SUBCOMMITTEES

3.1 Overview

Subcommittees are the policy-making Working Groups of the EDRN and report to the SC when requested by the Chair. Subcommittees meet twice a year in conjunction with the SC business meetings. Conference calls are made any time on the recommendation of the Chair of either the SC or Subcommittees. Formal meetings between the semiannual meetings require approval by the Chair of the SC.

Voting members of the Subcommittees are Principal Investigators in the EDRN. Co-investigators, Associate Members, and other interested parties, however, are welcome to attend Subcommittee meetings as consultants. The Chair of the SC appoints members to the Subcommittees although SC members can express their preferences on which Subcommittee they would like to serve. Members cannot serve on more than one Subcommittee simultaneously. Members are appointed for 2.5 years and can be re-appointed for a second, 2.5 year term. Each Subcommittee member has one vote. Consultants for Subcommittees can be appointed by the Chair of the SC or by the Chairs of the Subcommittees as non-voting members.

3.1.1. Chairs

The Subcommittee Chairs and Co-Chairs are appointed by the Chair of the SC and must be EDRN Principal Investigators. Term of office is 2.5 years with eligibility for reappointment for one additional consecutive term (for a total of 5 yrs). It is the duty of the Subcommittee Chairs to determine whether a quorum is present before opening the meeting. The Chair has the responsibility to prepare the agenda and to report to the Steering Committee.

3.1.2. Quorum

A quorum for all Subcommittee meetings, including conference calls, is defined as the presence of the majority of the voting Subcommittee members. If a quorum is not present, the meeting or conference call will be cancelled.

3.2 Collaboration and Publication Subcommittee

3.2.1. Objective

The objective of the Collaboration and Publication Subcommittee is to define procedures and conditions for formal collaboration within the EDRN and with investigators outside the Network, and define publication policies.

3.2.2. Responsibilities and Privileges

- Develop procedures for formal research collaboration within and outside the EDRN, including collaboration with individual investigators, industry, academic centers, community hospitals, government agencies, international investigators, and Cooperative Groups
- Determine collaborative relationships with private industry, especially with regard to IP issues
- Develop procedures for collaborating with other NCI Programs, such as SPORE, CGAP and the Cancer Family Registries
- Determine the role of the SC in monitoring collaborative research within and outside EDRN
- Develop guidelines for order of authors, standard credits, statement for source of support, and common formats for the publication of EDRN research
- Assist in developing common EDRN materials needed for obtaining approval for EDRN studies from Institutional Review Boards

3.3 Technology and Resource Sharing Subcommittee

3.3.1. Objective

The objective of the Technology and Resource Sharing Subcommittee is to establish the rationale and conditions for sharing technology and other resources among investigators within and external to the EDRN.

3.3.2. Responsibilities and Privileges

- Develop guidelines for sharing novel technology, reagents, and resources within the EDRN
- Develop guidelines for external Network sharing
- Develop guidelines and responsibilities for considering IP issues

3.4 Communication and Workshop Subcommittee

3.4.1. Objective

The objective of the Communication and Workshop Subcommittee is to achieve the full potential of biomarkers as tools to facilitate early detection of cancer by disseminating research goals and findings with the broader research community. To accomplish this objective, the Communication and Workshop Subcommittee defines formats for exchange of scientific findings such as workshops, seminars, and electronic information resources that serve to inform the research communities of scientific advances.

3.4.2. Responsibilities and Privileges

- Organize workshops to inform other components of the research community of the opportunities and needs to implement biomarkers in clinical screening, clinical trials, and early detection, etc.
- Develop long-term strategies that facilitate the translation of research advances into screening and detection practices
- Identify mechanisms to extend biomarker research to enable commercial development of diagnostic tools through public-private partnerships or collaborations
- Interact with organizations that facilitate the use of biomarkers in the clinical arena and discuss the long-term implications of biomarkers as screening and detection tools in population health
- Identify key audiences to engage/inform about EDRN research activities, goals, etc.
- Communicate with oncology groups, cancer research societies, immunology, biochemistry, pathology groups, epidemiology and biostatistical communities, biotechnology/bioengineering developers; technology transfer offices, voluntary health organizations, public health organizations, managers of health care, and regulatory agencies, etc.
- Organize workshops to inform other components of the research community of the opportunities and need to implement biomarkers in clinical screening, clinical trials, and early detection, etc.
- Develop other communication mechanisms to facilitate information dissemination (e.g., electronic media (websites, listservs) for communication among centers, data registries, newsletters, supplements to journals).
- Oversee liaisons

3.5 Prioritization Subcommittee

3.5.1. Objective

The objective of the Prioritization Subcommittee is to establish procedures for prioritizing research and allocating resources within the Network.

3.5.2. Responsibilities and Privileges

- Define the decision criteria needed for the evaluation of biomarkers beyond the discovery stage and set up a review process for implementing them in the EDRN
- Develop guidelines for coordinating the prioritized projects across the Network including obtaining involvement of the NCT
- Establish guidelines for utilization of the Core Funds and allocation of research resources
- Ensure integration of various components of the EDRN with the NCI Bypass Budget

- Develop metrics for evaluating the progress (success) of EDRN. Establish annual and overall milestones for EDRN that will be used for evaluating Network progress and reporting to the NCT, NCI Executive Committee, NCI Board of Scientific Advisors, and National Cancer Advisory Board

3.6 Data Sharing and Informatics Subcommittee

3.6.1. Objective

The objectives of the Data Sharing and Informatics Subcommittee are to establish guidelines for the EDRN data structure and common data elements, and to provide a forum for biostatisticians/analysts within EDRN to collaborate on research pertinent to EDRN.

3.6.2. Responsibilities and Privileges

- Develop EDRN Informatics Enterprise System compatible with NCI Informatics Enterprise and NCI standards (caBIG and CTEP systems)
- Develop guidelines for security levels of the centralized database
- Develop guidelines for internal and external data sharing that include mechanisms to ensure that the data are used appropriately
- Develop guidelines for statistical design and evaluation of biomarkers
- Monitor the quality of biomarker data captured and curated in biomarker database
- Develop guidelines for posting materials on the secure website
- Review patient privacy requirements for EDRN in conjunction with the relevant Subcommittee
- Develop methods to promote data sharing with NCI programs such as CGAP, CGN, SEER, etc.

SECTION 4 GROUPS

4.1 Standing Review Group

The Standing Review Group is responsible for reviewing Associate Membership applications. Members are nominated by the Chairs of the Collaborative Groups and/or NCI Program and appointed by the Chair of the SC. The Group consists of two Principal investigators from each of the Collaborative Groups (one Principal Investigator from a BDL and one Principal Investigator from a CVC), one Principal Investigator from a BRL, the Principal Investigator or designee from the DMCC, and one representative of the NCI Program. Additional EDRN and non-EDRN consultants can be added at the discretion of the EC. Details on the application and review processes are under the 'Policies and Procedures' section of this manual. Term of office is 2.5 years with eligibility for reappointment for one additional term (for a total of 5 yrs).

SECTION 5 ACTIVITIES TO PROMOTE COLLABORATION

5.1 Collaborative Groups

Collaborative Groups are organ-specific groups designed to promote the exchange of information on organ related biomarkers and identify research priorities within EDRN. Members of the Collaborative Groups are the members of the SC, their co-investigators, Associate Members, and other interested parties. Members are encouraged to participate on the Collaborative Group that best reflects the expertise presented in their original peer-reviewed application. Members cannot serve on more than one Collaborative Group simultaneously. There are four Collaborative Groups: Breast/Gynecology, Prostate and Urologic, Lung and Upper Aerodigestive Tract, and G.I. and Other Associated Cancers.

5.1.1. Responsibilities and Privileges

- Conduct routine literature reviews
- Write manuscripts describing the current state of biomarker development
- Review pre-proposals for EDRN Validation Studies
- Create opportunities for collaboration within each organ-based groups
- Provide leadership for identifying the most promising biomarkers

5.1.2. Chairs

The Collaborative Group Chairs and Co-Chairs are appointed by the Chair of the SC and must be EDRN Principal Investigators. Term of office is 2.5 years with eligibility for reappointment for one additional term (for a total of 5 yrs). It is the duty of the Collaborative Group Chairs to determine whether a quorum is present before opening the meeting. The Chair has the responsibility to prepare the agenda and to report to the Steering Committee. Former Chairs are ex officio members.

5.1.3. Quorum

A quorum for all Collaborative Group meetings, including conference calls, is defined as the presence of the majority of members. If a quorum is not present, the meeting or conference call will be cancelled.

5.2 Liaison Members

The purpose of liaison members is to ensure that members of key scientific organizations are aware of EDRN activities and to ensure that EDRN members are aware of activities of outside organizations that may impact EDRN. Liaison members to scientific and professional organizations, including scientific programs at NCI, are appointed by the Chair of the SC. Liaisons are appointed to 2.5 year terms with eligibility for reappointment for another two-year term. Liaison members report to the SC on activities by other organizations that are relevant to the EDRN during the semiannual SC meetings.

5.3 Sponsor

- Act as spokesperson for the Associate Membership
- Keep track of members progress
- Shares significant progress with SC and EC when called for
- Participate in evaluating the progress at the end of the grant period

SECTION 6 POLICIES AND PROCEDURES

6.1 Associate Membership

The Associate Membership is designed for investigators who are not affiliated with EDRN and wish to propose collaborative studies within the scope and objectives of the EDRN. There are three categories for Associate Membership. Associate Members are welcome to join a Collaborative Group on the basis of their expertise and interest.

Category A Members are domestic or foreign investigators who propose to conduct basic or translational research consistent with the priorities of the EDRN. Supplemental funds provided through Category A Membership are to be used as one-time "seed money" for pilot studies necessary to support applications for future independent funding. Funds are provided for a period of two years and are not renewable. Although support of Category A Members ceases after two years, they are considered to be Associate Members for the duration of the EDRN. Category A Associate Members are invited to participate in Workshops and Steering Committee meetings. The "seed money" will be $50,000 direct costs per year for two years with additional “Facilities and Administrative” costs (F&A costs). The applicants must include in the budget funds to attend two EDRN SC meetings per year.

Category B Members contribute to the Network by sharing available technologies, contributing specimens, making available high-risk registries and cohorts, and providing other resources complementary to the Network and in conjunction with biomarker validation studies. They can be domestic or foreign. Category B Members can reapply for project-specific funds annually (total funding amount should not exceed $100,000 in direct costs with additional “F&A costs”, unless the Network needs as determined by the EC justify additional funding). Category B Members are considered Associate Members after funding ceases for the duration of the EDRN. Category B Associate Members are invited to participate in Workshops and Steering Committee meetings. Any clinical or laboratory site (other than current BDLs, BRLs and CVCs) participating in a validation study are considered Category B Members.

Category C, Corresponding Members, are scientists, organizations, clinicians, patient advocates, or ethicists who are interested in participating in Collaborative Group meetings and EDRN Workshops and Conferences yet do not receive funds from the EDRN. Category C Members will be invited to these meetings and conferences, but their expenses will not be supported by the EDRN. Category C members can be domestic or foreign. The application for Category C Members is the similar to that of other Associate Member applicants, with minor modifications: the budgetary document can be disregarded, and the proposal in the form of a letter addressed to the EDRN EC should explain how the applicant’s participation at the meetings, workshops and other Network activities will contribute to the mission of EDRN. Category C Members are considered Corresponding Members for the duration of the EDRN. EDRN Members for which funding has ceased are considered Category C Members for the duration of the EDRN.

To apply for an Associate Membership, applicants must be sponsored by an EDRN Principal Investigator. For details on the application procedure please see the EDRN website: http://edrn.nci.nih.gov/.

NIH policies (http://deainfo.nci.nih.gov) are observed for accepting revised applications. The number of amended (revised) versions of an application is limited to one, and this must be

submitted within two years of the original submission. The Introduction must also include responses to the main criticisms and issues raised by the reviewers.

The Standing Review Group's comments should be included in the revised application packet. The application must include an Introduction of not more than 1 page that summarizes substantial additions, deletions, and changes. The Introduction must also include responses to the criticisms and issues raised by the reviewers.

Associate Members will agree to follow EDRN policies and procedures and include a copy of their annual progress report to their Sponsor and NCI.

6.1.1. Responsibilities of the Sponsor

Sponsors of Associate Members are responsible for submitting the initial membership application, representing their interests in SC meetings, and inviting them to EDRN meetings.

Sponsors are responsible for ensuring that their Associate Member is accountable, follows all EDRN policies and procedures, and, if requested, provide an update on their Associate Member's progress.

6.2 Funds

6.2.1. Definitions

There are two sources of funds available through EDRN: Restricted Funds and Steering Committee Core Funds.

Restricted Funds are funds that are set aside from the annual budget of BDLs, BRLs, DMCC and CVCs for Collaborative Studies.

- After the first year investigators from BDLs and CVCs must set aside 30% of their annual budget for Network Collaborative Studies.
- Investigators from BRLs must set aside 30% for collaborative studies. Collaborative studies must be submitted as part of a team of BRL or with at least one other component of EDRN (BDL and/or CVC). Funding for multiple years will be allowed subject to annual approval and the completion of the interim milestones approved for the project. The use of set-aside funds will be restricted to collaborative projects relevant to the Network's objectives, and must be reviewed and approved by the EDRN EC and the NCI.
- Investigators from BDLs and CVCs must set aside 30% of their annual budget after the first year for Network collaborative studies. The reimbursement will be based on the complexity and amount of clinical data, specimen types, duration of follow-up, and other factors within collaborative studies as decided by the Executive Committee.
- The DMCC must set aside 30% of its funds for Validation Studies.

Applicants for the release of Restricted Funds must include their specific plans for responding to the terms and conditions section of their grant award notice. The use of these set aside funds is

restricted and must be reviewed and approved by the EDRN EC and then recommended to, and approved by the NCI before release from the individual U01 or U24 awards.

Steering Committee Core Funds are reserved for post-award collaborative Network research and for expanding participation within the Consortium. These funds can also be used to assist in moving a marker through the validation process. Examples of validation funding needs include accrual of patients, scaling-up of reagents, contracting to other laboratories or companies to scale-up production and maintain the quality of reagents. Funds can also be used for data management, travel, meetings, and other collaborative activities of the Network.

6.2.2. Release and Use of Restricted Funds

A Principal Investigator may only apply for the Restricted Funds within his/her Cooperative Agreement award. Restricted Funds may only be used for projects that complement the scope of the Cooperative Agreement award and/or support an approved EDRN Validation Study. More than one investigator may request the release of Restricted Funds for one collaborative project. A Principal Investigator may apply for more than one year's Restricted Funds, however, a status report must be submitted to NCI and should specifically detail how the Restricted Funds were used before subsequent year funds are considered for release. The status report may be submitted as part of the annual progress report submitted by the Principal Investigator. The applications for the release of Restricted Funds are reviewed by the EC at their monthly meetings. Applicants must apply for renewal within 90 days of their anniversary date of their Type 5 application. Validation Study applications for release of set aside funds are considered priority over other requests.

6.2.3. Application Requirements for Release of Restricted Funds

The application for release of Restricted Funds includes the EDRN Study Proposal Application Form and a proposal. The proposal must be single-spaced and follow NIH Format, as used in PHS Form 398. It should be organized and submitted as follows:

1. EDRN Study Proposal Information Sheet (located on secure website)
2. Title Page (page 1 of the PHS Form 398). Description (Abstract), Performance Sites, and Key Personnel (use page 2 of the PHS Form 398). Bibliography of key researchers involved (use page 6 of PHS Form 398).
3. Scientific Proposal and References (up to 5 pages), organized into Rationale, Goals, Sample Size, Preliminary Data (optional), Technologic Design and Approaches, Contribution to Translational Research, and EDRN Specific Aims/Deliverables. Address review criteria as established by the EDRN Steering Committee (see Review Criteria section below).
4. Budget Page - (final page unless an Appendix section is included). Use page 4 of the PHS Form 398. Adequate budget justification for direct costs is required.
5. Appendix (optional).
6. One electronic copy of the proposal should be submitted to the NCI EDRN Program Office.

All projects must comply with institutional regulations on research involving human subjects, children, minority groups, gender, animals, recombinant DNA, and hazardous materials.

Appropriate approvals from the relevant committees, including approval from institutional review boards, must be submitted to the NCI EDRN Program Office before funds can be provided for successful applications.

6.2.4. Application Requirements for Release of Developmental Funds

Applicants should clearly define the research objective for the first year, which will be peer-reviewed by the scientific review committee. Support for subsequent years will be reviewed by the EDRN SC, which will make recommendations to the NCI. Prior to proposing the developmental study, applicants are encouraged to contact the program officials listed on this RFA to discuss the needs of EDRN in the area of technology and assay refinement.

6.2.5. Review Criteria

Definition: Set-asides funds are restricted funds that are awarded to an individual grant. The primary purpose of the set-aside fund (see RFA CA-14-014 CA-16-009 is to promote the laboratory/center participation in the Network-wide Validation Studies. In absence of such a study, the funds are considered for inter- EDRN or external collaborative studies. An intra-EDRN study is of higher priority. The proposed project should capitalize and leverage on the EDRN-established infrastructure and resources. Two major criteria must be met before recommending the release of restricted funds: scientific significance and collaborative strengths.

Review criteria for release of Restricted Funds or Core Funds for Associate Membership category A or B are based on scientific merit and compatibility with EDRN objectives.(see Appendix 3 and 4) Seven formal criteria are used to assess the suitability of proposals for supplemental support and/or advancement to the large-scale validation phase:

- Scientific merit
- Study design: e.g., prospective versus cross-sectional
- Technical parameters: reproducibility, sensitivity, specificity, throughput, automation, and cost
- Clinical or scientific impact: e.g., more common cancers or a significant impact in less common neoplasia
- Portfolio balance within EDRN and NCI's need
- Practicality and feasibility: e.g., required sample size, amount of tissue
- Collaborative strength, including contribution of resources and technology. Collaboration is a central mission of EDRN.

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 may be a critical component in an overall plan to achieve EDRN goals and may represent a high level of cooperation and interaction among investigators toward EDRN objectives.

Additional Information on Review Criteria

Significance:

The application must clearly state the scientific merit of the proposal.

Does the proposed research convey the urgency of scientific needs in the area of biomarker-based diagnostics possible only through a collaborative approach?

Will the approaches advance the field of biomarkers/reagents development in the context of cancer detection and risk assessment?

Does the proposal uniquely discuss challenges and issues relevant to cancer detection and screening?

Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

How would the proposed research complement or augment existing detection systems or methodologies?

Is the proposed approach or technology adaptable, or does it have the potential to analyze large samples in a population setting for screening purposes?

What is the immediacy of the research opportunity in light of the EDRN-established phases of biomarker development for early detection of cancer and potentials for moving biomarkers to Phase II or Phase III?

Does the applicant have demonstrable evidence for bringing biomarkers to Phase II or Phase III? This is particularly important for an analytical validation study.

To what extent are the specific aims integrated to address the proposed goals?

Collaborative Strengths:

The application must clearly state the need for such a collaboration and reason as to why this study requires collaborative platforms (expertise, infrastructure, resources) of the EDRN.

Are plans for collaborations provided for research objectives?

To what extent are these collaborations necessary for the successful completion of the research plan? Only projects of collaborative nature are to be supported through the restricted funds.

Do the proposed experiments take advantage of unique features of the EDRN scientific environment and incorporate the best use of collaborative arrangements?

Will this team of investigators contribute unique skills to the proposed project?

Do the investigators state their willingness to collaborate and share information?

Are there adequate plans for effective interaction and coordination with the Network components, such as the SC, the DMCC, or the NCI?

In case of genomic and proteomic profile studies, investigator will be required to post data on the EDRN Secure Portal.

Portfolio Analysis: (for program review only)

NCI program staff will evaluate each application relative to other research projects being conducted within EDRN to ensure there is a fair representation of technologies and cancer types. Under or over representations will be included in determining the final recommendation. In addition, proposal will be reviewed for:

Does the proposal compete against any already funded approach within the EDRN systems? If so, what is the added value?

Does the proposal fall under the NCI's Strategic Initiatives? To what extent is it supported by any other program, such as IMAT?

Budget:

The applicant's budget must be justified in light of the scope of the work and must not exceed the set-aside [Program is to keep track of this amount]. The reviewers may recommend a budget less than the set-aside.

6.2.6. Application Requirements for Use of Core Funds

Requests for Core Funds can be made by EDRN investigators to conduct collaborative projects involving and focusing on EDRN objectives, to advance current projects toward validation, or to conduct a Validation Study. Budgets must not exceed $100,000 unless sufficient justification is provided, or for an approved large validation study. Adequate budgetary information should be provided to justify proposed spending. Applications for Core Funds are accepted the first week of each month and are reviewed during monthly EC calls held the last week of the month.

EDRN investigators applying for funds to conduct collaborative projects must complete both the EDRN Study Proposal Application Form and a proposal following the format of PHS Form 398 as described in Section 6.2.3. Applicants for Associate Membership need only submit a proposal following the format of PHS Form 398 (see Section 6.2.3). All projects must comply with institutional regulations on research involving human subjects, children, minority groups, gender, animals, recombinant DNA, and hazardous materials. Appropriate approvals from the relevant committees, including approval from Institutional Review Boards, must be submitted to the NCI EDRN Program Office before funds can be provided.

6.2.7. Review Process for Type A and Type C Associate Membership Applications

The EDRN Standing Review Group will review all Type A Associate Membership applications. The EDRN EC will perform an accelerated review of applications for Associate Membership (Category C) that do not seek funds from EDRN. The specific criteria used to evaluate proposals for use of Core Funds are listed in the section above, Section 6.2.4. The review process is described below*:*

1. The electronic Associate Member applications received by the receipt date are forwarded from the NCI EDRN Program Office to the members of the EDRN Review Group within a week after the application receipt date.
2. The EDRN Standing Review Group evaluates Associate Member applications in a telephone conference call, and then scores the applications via a secure online review process on the EDRN secure website. The NCI EDRN Program Director is able to read all reviewers' comments and consolidates them. The evaluation and compilation of comments is expected to be completed within one month following the application receipt date. After compilation of comments, the EC members are notified that consolidated comments and scores are ready for their review.
3. The Executive Committee renders final approval of the reviewed proposals, informs the Steering Committee of successful applications, and submits the recommendations to the NCI EDRN Program Office.
4. The EDRN Chair's institution contacts NCI Grants Administration Branch by letter, requesting approval to release the restricted funds. Once the NCI Grants Administration Branch receives all approvals, NCI authorizes the release of funds.

6.2.8. Review Process for Validation Study Proposals

The EC will review Validation Proposals and other collaborative projects that seek Core Funds, including Type B Associate Membership applications, and may seek advisement from the relevant Collaborative Group on the merit of the proposal prior to its discussion at the EC. If necessary, it will appoint an ad hoc committee that will include at least one member from the appropriate Collaborative Group.

Progress of a biomarker to a validation study is a critical step in the development of a biomarker and is, therefore, a critical part of EDRN. Applicants are encouraged to submit their validation study proposal to the relevant collaborative group and seek their concurrence before the EC reviews their proposal.

1. **Pre-proposal:**

   A pre-proposal/letter-of-intent, limited to 5 pages, must be submitted to the appropriate Collaborative Group Chair or directly to the EC. Validation Studies are collaborative, therefore, the pre-proposal must name the EDRN sites which will be included as part of the collaboration. A Biomarker Reference Lab and the Data Management and Coordinating Center must be consulted for all Validation Studies. A Clinical Validation Center should be included as needed.

   The Collaborative Group Chair will disseminate the pre-proposal amongst Collaborative Group members for discussion and recommendation. Applications submitted directly to the EC may be reviewed by the EC or referred to the appropriate Collaborative Group for review. If approved by the EC, the submitting investigator will be asked to complete a full proposal as described below and submit it to the NCI EDRN Program Office.

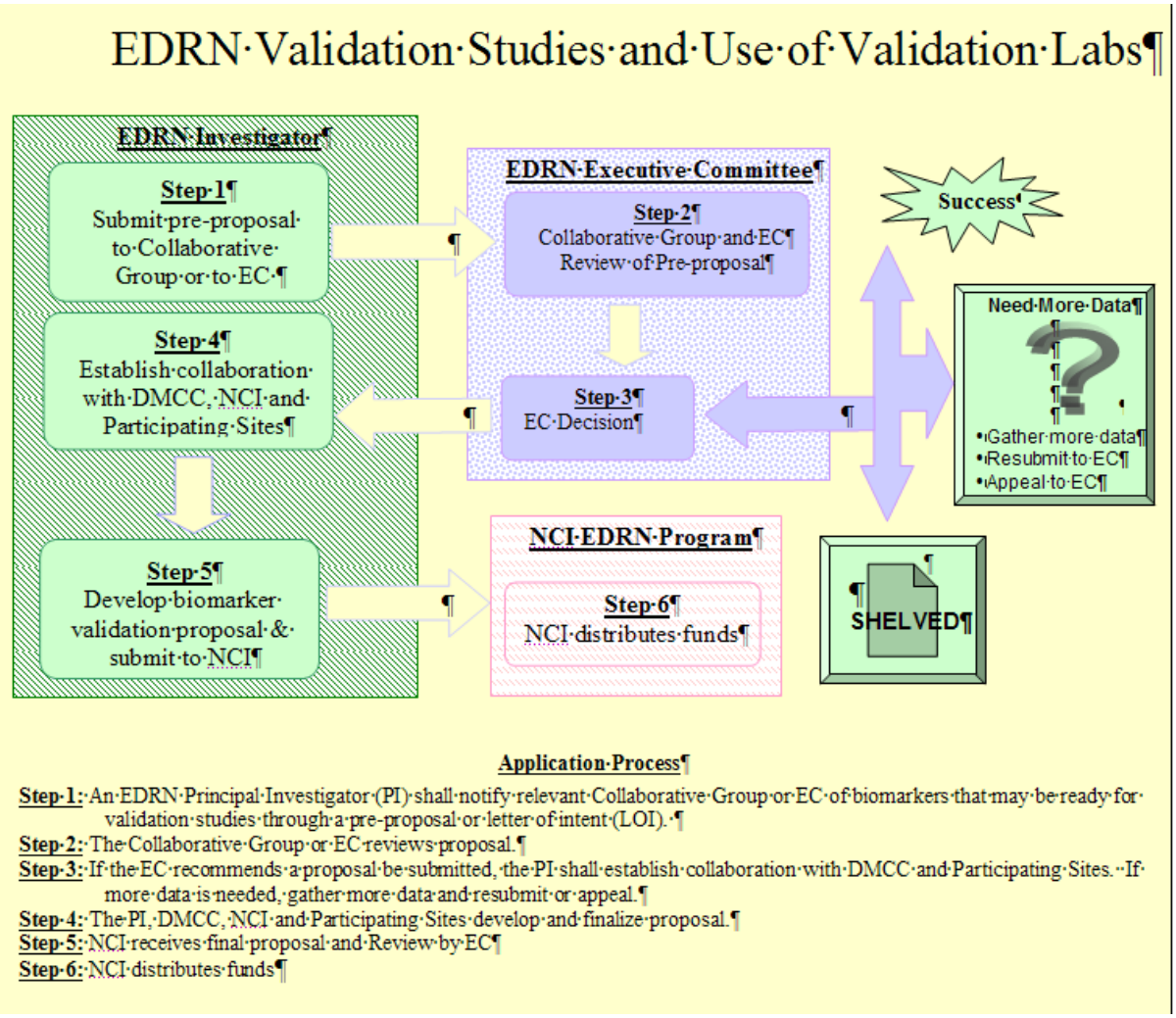
2. **Proposal:**

   Once the pre-proposal is approved by the EC, the investigator contacts a Biomarker Reference Lab, Data Management and Coordinating Center, and/or Clinical Validation Centers, as appropriate for collaboration, and develops a full proposal with them. The

full proposal should be prepared as described in Section 6.2.3 with the exception that it should not exceed 20 pages rather than 3 pages. A detailed background and rationale are not necessary but presentation of preliminary data is required.

Full proposals are submitted to the NCI EDRN Program Office. The full proposal is evaluated by EC or appointed ad hoc committee and external reviewers (non-EDRN members). The remaining steps for the Validation Study review process are the same as steps 3 & 4 in Section 6.2.6.

See Appendix 5 for the policy regarding blinding of specimens for collaborative studies.



6.3 EDRN Standard Specimen Reference Set Guidelines

It is the goal of specimen reference sets to promote the aims of the Early Detection Research Network, i.e., testing and implementation of biomarkers useful for the detection of solid malignancies for the purpose of down-staging incident cancers in the population. Much of the biomarker work to date has been performed on convenience samples from cases and controls. Since these samples have been collected in a variety of ways, comparisons have been difficult. Further, cases and controls may not have been selected and matched using appropriate rigor to reduce bias. Finally, since there has not been a common resource with sufficient amounts of sample, comparison or integration of multiple markers has not been feasible. With the creation of shared and common sets of specimens from well characterized and matched cases and controls from specific disease spectra, the EDRN will overcome many of the logistic and design issues in preliminary and advanced biomarker validation. This resource will be accessible to any investigator within or outside of the EDRN based upon a common and transparent set of criteria used to evaluate applications. It is anticipated that results from these studies will be made publicly available.

The Specimen Resource Sharing Committee was created within the EDRN to draft a process through which these specimen reference sets could be accessed. It is the opinion of this committee that no completely common set of criteria could be used to evaluate biomarkers from the disparate cancers encompassed by these sets. Each cancer site has its own particular requirements, barriers, and opportunities for detection. Therefore, the appropriate organ-specific Collaborative Group should handle the detailed scientific evaluation of applications for samples. However, it was also recognized that certain common guidelines and procedures could be developed and implemented without reducing the scientific and programmatic input of the Collaborative Groups. After providing specific details related to the specimen reference set(s) being requested and institutional approval to use these sets, the investigator is then expected to address the following topics as provided on the application form (see Appendix 6) in relation to his/her biomarker and future intentions:

- Clinical Relationship
- Background and Significance
- Preliminary Data & Methods
- Data Analysis Plan
- Collaboration
- Future Plans

If additional review criteria or application queries for any specimen reference set are stipulated by the corresponding Collaborative Group, the appropriate NCI Program Director will provide this additional material to the investigator. In essence, each Collaborative Group will determine the stringencies for granting access to specimen reference sets they have oversight of. These standards should be established by the Collaborative Groups before the set(s) become available. For each review conducted, it is expected that every Collaborative Group will include an adequate biostatistical critique, either from within a participating laboratory of the Collaborative Group, or by involvement of the DMCC, to ensure that appropriate consideration is given to statistical concerns of the proposal.

Upon receiving an inquiry or request regarding access to specimen reference set(s) the appropriate NCI Program Director will be notified to send an application form and any other relevant documents to the investigator. After the completed application has been returned, the Program Director will then forward it to the respective Collaborative Group. The Collaborative Group, in a timely manner (within one month) will review and discuss the application and offer a recommendation of whether 1) the investigator should be sent the requested specimen reference set(s), 2) further clarification or revision are needed, or 3) the request is deemed to be of low priority and deferred or denied.

1. If approval is given, the EDRN Executive Committee will be notified at its next monthly meeting by the Collaborative Group chair (or co-chair). If extenuating circumstances require a more timely response, the Executive Committee will be notified by email of this decision and the Committee must respond to the Collaborative Group chair within 48 hours if they have any concerns. As the Executive Committee provides oversight for global EDRN activities, it needs to be informed of requests for specimen reference sets that have been received and reviewed within EDRN. In principle, the Executive Committee will concur with all approvals recommended by Collaborative Groups unless special issues are raised. NCI Program Staff will then notify the facility in Frederick to prepare the materials needed for sending the appropriate specimen reference set(s).
2. If further clarification is needed, the Collaborative Group will inform the Program Director of what concerns or questions remain with the application. The Program Director will then communicate with the investigator of these issues to ask for a resubmission.
3. If deferral or denial is made, the Collaborative Group will provide the rationale to the Program Director why the request was turned down. The Program Director will then relay this decision and its reasons to the investigator.

See Appendix 7 for EDRN Pre/Validation Reference Set Specimen Sharing Guidelines)

6.4 EDRN Informatics

6.4.1. EDRN Secure Website

6.3.1.1 Overview

The Data Management and Coordinating Center (DMCC) is responsible for developing and maintaining a secure website for EDRN. The website contains general EDRN 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, paper drafts, etc. Due to the sensitive nature of some of the information available on the secure website, only people approved by an EDRN member have access to the website. Access to the website requires a log-in and password distributed by the DMCC.

A website user's guide is provided in Appendix 9.

6.3.1.1 Obtaining A Log-In And Password

In order to obtain access to the secure website, one must complete the Application for EDRN Secure Web Site Access (see https://edrn.nci.nih.gov and follow the Log in link) and PDF the completed form and send it to the DMCC Project Manager at jdahlgre@fredhutch.org. The application form must be signed by an EDRN Principal Investigator. Once the application is processed at the DMCC, the applicant is sent a log-in via email and a password via separate e-mail. The log-in name generally consists of the applicant's first name initial and entire last name. The same username and password is used for the Secure Website and the secure features of the Public Portal.

6.3.1.1 Passwords and Security Issues

Once an applicant receives their password, the website will prompt the user to change their password at first login. A user can change their password at any time by clicking on "Change Password" at the bottom of any page on the website. For security reasons, passwords for the EDRN secure website must adhere to the following guidelines:

1. May not contain all or a part of the username
2. Must be at least 8 characters in length
3. Must contain characters from three of the following categories: Uppercase letters, Lowercase letters, numbers, non-alphanumeric characters (like # and !)
4. Cannot reuse the last 5 passwords
5. Cannot change a password more than 5 times per day

After the user has changed their password, they will be asked 2 personal questions which, when answered correctly, will retrieve their password in case they forget it or need to confirm it.

The DMCC also recommends that public personal data (e.g. name, birthday) should not be used in passwords. Log-in IDs and passwords should also be kept in a safe place. To maintain compliance with the DMCC's IRB, you may not share your password or log-in.

Each user's password will expire every four months. If a person enters his/her log-in and the password has expired, s/he is prompted to change the password at that time. A log-in will lock after three failed attempts and then reset itself in 30 minutes. If this happens, please wait 30 minutes and then try to log into the web site again or contact the DMCC at edrndmcc@fredhutch.org.

6.4.2. Common Data Elements (CDEs)

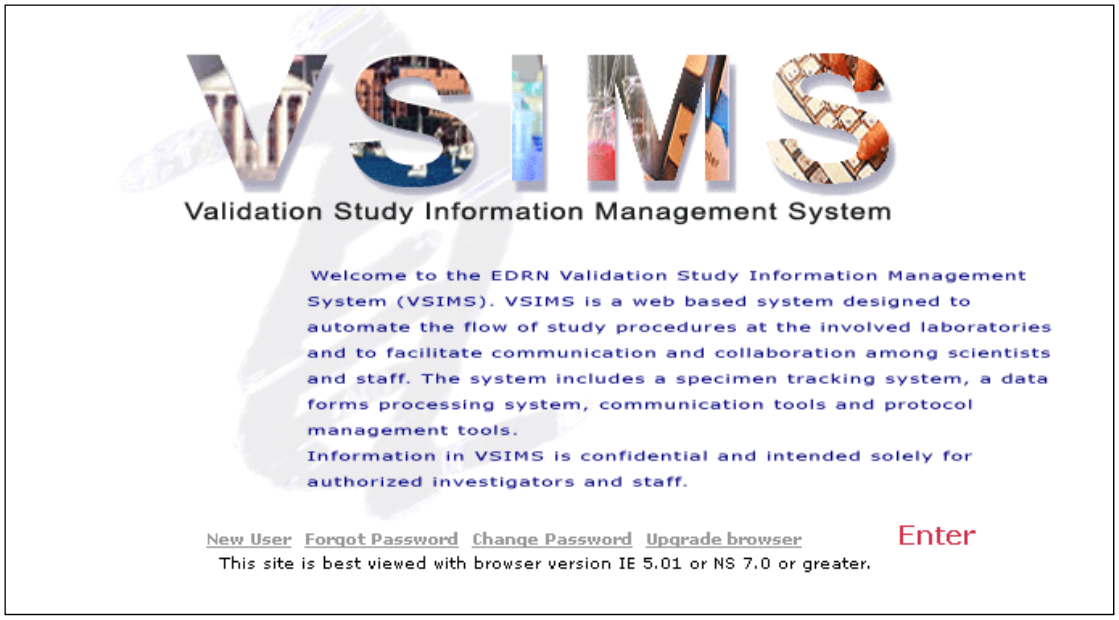
The EDRN Common Data Elements (CDEs) are composed of three main components: the exact wording of the questions used to collect data, all possible responses to the questions, and the data format for sharing and/or transmission of the data within EDRN. The CDEs will standardize data that is collected and stored at all sites to ensure consistency in data and specimen sharing.

Any EDRN sites collecting new prospective data for EDRN studies are required to use the EDRN CDEs.

Currently there are three categories of CDEs that have been developed to varying extents for EDRN. The first is the Core CDEs. The Baseline and Follow-up Core CDEs are comprised of a participant ID, protocol ID, site IDs and basic epidemiologic data relevant to EDRN. The Core Specimen CDEs include the specimens that are collected from a participant at each specimen collection date. The next category of CDEs is the Specimen type-specific CDEs and includes information on the processing and storing of the specimens that were collected. The last category is Organ-specific CDEs and consists of data elements important for organ-specific studies. The development of the Organ-specific CDEs requires the participation of the Collaborative Groups.

The CDE tools created by the Data Management and Coordinating Center (DMCC) enable sites to view all existing groupings of CDEs on forms, create and modify their own groupings on forms, and view all the information associated with the EDRN CDEs.

6.4.3. Validation Study Information Management System (VSIMS)



Validation Study Information Management System (VSIMS) allows for the efficient and secure collection and management of information for all EDRN Validation Studies. VSIMS is a secure web-based system that is designed to automate evaluation of eligibility criteria and data collection, transfer data, track specimens, serve as a resource for study-specific information, facilitate communication across multi-center studies, track data queries and resolutions, and allow administrative management of studies. The ability of the system to adapt to different sets of business criteria and workflows allows information to be stored separately for each study allowing multiple studies to be coordinated centrally through the same data management system framework. The greatest strength of the system lies in its flexibility and ease in making changes, enabling several Validation Studies to be simultaneously or consecutively implemented and managed in a timely manner. See Appendix 8 for the policy regarding the use of VSIMS for EDRN Collaborative Studies.

6.4.4. EDRN Catalog and Archive Service (eCAS)

The EDRN Catalog and Archive Service (eCAS) supports the capture and distribution of the published science data acquired during a validation study. The eCAS infrastructure will satisfy several EDRN informatics goals, including:

- Acquisition of published science data from multiple EDRN validation studies
- Software interfaces for sharing of data across biomedical applications
- Secure transfer and distribution of data to the science community
- A common information model for describing EDRN science data
- A web-based interface to search and download EDRN science data

The EDRN Informatics Working Group is currently prototyping the eCAS to validate these goals. The prototype demonstrates how data acquired locally at institutions can be archived using the EDRN common information model and then distributed to scientists nationally through the EDRN Public Portal. Participating EDRN sites will also be able to catalog their science results remotely with the eCAS system via the Public Portal. The common science portal will provide access to all published EDRN science data enabling distribution to a broad range of users using a well-defined security access policy.

6.4.5. Biomarker Database

The EDRN Biomarker Database (BMDB) is currently being constructed to capture and catalog biomarker annotations and related ancillary data from biomarkers pursued within EDRN and elsewhere. Biomarker data and results will be curated into the BMDB including links to study protocols, publications and other related information and resources from multiple EDRN and non-EDRN databases. BMDB will also support access to raw biomarker data for the purposes of statistical analysis and meta-analyses.

6.4.6. Public Portal

The principal focus on the EDRN Public Portal is to raise the awareness of the EDRN by the public through a web portal. It provides an online mechanism to distribute information and results from the EDRN to the public. This includes news, announcements of opportunities, availability of online data sets, information about EDRN studies, access to various EDRN resources, and overall information about the EDRN program. The Public Portal also serves as a gateway to other EDRN tools including eCAS and ERNE. It provides a publishing capability so that new information can be easily reviewed and published to the portal.

6.4.7. EDRN Resource Network Exchange (ERNE)

EDRN has deployed the EDRN Resource Network Exchange (ERNE) to ten institutions providing a common web-based client interface. ERNE unifies search and retrieval of biospecimen data from all institutions regardless of where it is located, how it is stored, or the differences in the underlying data models. This enables a scientist, for example, to locate tissue specimens for breast cancer by searching data catalogs at participating institutions across the country.

As the knowledge system evolves, the governing CDE model and the use-cases derived in the working groups will be used to drive the relationships between the data sets enabling discovery through data mining. Scientists, for example, will be able to query an assay result from a validation study and then find the associated specimens that were collected as part of that assay.

6.4.8. EDRN Study Information System (eSIS)

eSIS is a subsection of the EDRN Secure Website that is used to monitor progress of all EDRN projects (single site, collaborative and network collaborative). It is the responsibility of the Principal Investigator(s) to maintain accurate content as well as track milestones.

SECTION 7 EDRN PROGRAM EVALUATION

7.1 Metrics for Evaluation

7.1.1. Objectives

It is the responsibility of the awarding agency, in this case the National Cancer Institute (NCI), National Institutes of Health, to review progress achieved towards scientific goals in original grant applications over specified grant periods and to provide scientific and logistical input to grantees to enhance the quality of their scientific efforts. For details, see HHS 45 CFR, Part 74. To review progress towards achieving the objectives of the Early Detection Research Network (EDRN) and its investigators, it is imperative for EDRN program officials to gather information on the functioning of the network in order to update the NCI leadership. This document describes metrics, rationale, and standards for evaluating the overall success of the EDRN.

7.1.2. Introduction

Fair, rigorous peer review of investigator-initiated scientific applications remains the cornerstone of scientific progress in the United States. Peer review has ensured that the best science is supported. The EDRN was initiated with this concept in mind. By selecting scientific collaborators for the EDRN on the basis of rigorous peer review and fully funding the best applications, the NCI has successfully obtained strong participation from the scientific community.

The EDRN represents a major pioneering effort in collaborative translational research. It departs from prior Cancer Cooperative Group models in many important ways - through empowering investigators by funding their Centers directly and by placing the burden of scientific leadership, research agenda, and collaboration upon these directly funded Centers. Basic scientists with robust bench research records have been funded to pool their ideas, resources, and tools. Translational and epidemiologic investigators with strong tools and publication track records are directly funded with a mandate to translate concepts arising from basic science labs. Analytical tools, laboratories, statistical methods, and informatics are also supported directly with a collaborative mandate. Leadership of this collaborative must emanate from the grass-root investigators, and the Executive Leadership must communicate with a highly knowledgeable group of scientists in a manner that enhances collaboration and productivity. This Network represents a new paradigm of Cooperative research.

7.1.3. NCI Charge to the EDRN

NCI leadership and Program Staff have provided the following charge for this collaborative enterprise:

- Establish criteria for the discovery and validation of biomarkers at all points of the integrated research scheme;
- Establish a rigorous quality assurance/quality control program for biomarkers;
- Establish and deal with issues of biorepositories -- how the samples will be obtained, stored and most importantly, allocated;

- Support Translational Research Projects-both within and outside the EDRN - and establish policies and procedures that are inclusive of investigators who wish to utilize the infrastructure and facilities of the EDRN;
- Establish and foster industrial collaborations which will be crucial to the ability to rapidly translate the research effort into products and to test innovative biomarkers being developed by industry;
- Establish and maintain effective and efficient communications, including the use of EDRN websites (public and private), listservs, email, and regularly scheduled meetings;
- Develop and maintain an effective, efficient, and productive management domain with minimal committee structure and maximal collaboration, with financial rewards for collaboration;
- Encourage inclusiveness by ensuring that scientists with promising research ideas get the opportunity to collaborate constructively with the EDRN.

7.2 Evaluation Metrics

Since there are no prior models of such a cooperative research enterprise, it is very important to carefully monitor and assess progress from both macro and micro perspectives. Substantial administrative effort will be expended in order to build and expand this infrastructure. The following evaluation metrics are suggested.

7.2.1. For the Individual Laboratory and Center

1. Scientific Excellence

   Quality of Questions: Has the EDRN site clearly defined their objectives, hypotheses, and scientific plan?

   Scientific Progress to Date: Has the EDRN site made progress towards meeting these objectives as specified in their originally funded research plan? What pitfalls have been encountered and how have they been managed?

   Innovation: How has the EDRN site used innovation to overcome obstacles? Is the site aware of new methods or approaches that might be useful to or portable into the EDRN environment?

   Future Plans: What does the site plan to do over the coming two years? How will these plans meet the original grant objectives?

2. Productivity Metrics

   Publication productivity: Has the site published papers on the objectives funded by the EDRN? How many and in what Journals? If not, are there problems that need to be addressed or require assistance?

Grant funding: Has the site applied for additional grant or contract funding? Has the site team been successful in gaining additional funds? Has the EDRN been helpful to the success of funding these new grants or contracts?

Biomarkers identified (BDLs): Number of new biomarkers pursued for evaluation? Number of biomarkers sent forward to CVCs or BRLs for validation? Number of biomarkers added to early detection or risk assessment panels? Number of biomarkers used in chemoprevention clinical trials?

Assays performed (BRLs): Numbers of assays developed for EDRN projects? Numbers of samples processed? Types of samples processed? Results reported? Quality control of samples assayed? Number and type of development projects approved? Use of CDEs?

DMCC: Standards of informatics support? Type of informatics, QC procedures, patient privacy protection measures, data storage, and retrieval systems for Validation Studies? Development of Network-wide communication systems? Development of Network-wide systems to promote data and specimen sharing? Development of statistical methodology to meet the needs of EDRN?

Samples collected and provided (CVCs): Numbers of samples collected? Types of samples collected? Sources of samples collected? Numbers of samples provided to EDRN BDLs or BRLs? Use of CDEs? How many CVCs have had their set-aside funds released? How many CVCs have requested the release of Developmental funds?

3. Collaborative Metrics

EDRN collaborations: With whom is the EDRN site collaborating? How many projects are collaborative? How many joint papers have been published? Use of EDRN resources: Has the EDRN site collaborated with CVCs, a BRL or BDL site? If so, how many? Joint publications? Joint grants? How many BDLs have requested release of their restricted funds for Network Collaborative Studies?

Participation in EDRN Activities: Attendance from the site at EDRN meetings. Participation on Committees, working groups, and task forces? Special EDRN projects completed. Did EDRN site participate in developing the CDEs? Did EDRN site help to standardize/streamline the IRB approval process? Did EDRN site help develop systems for streamlining data sharing and/or specimen sharing? Did EDRN site help develop systems to standardize/streamline technology transfer issues?

EDRN outreach: Number of new Associate Members from the outside? Amount of core funds allocated to new Associate Members? The number of applications for core funding? Other outreach activities?

7.2.2. Process for Evaluating Metrics

1. Annual written progress report

Reviews should be based upon the yearly progress report required for non-competitive renewal. Instructions for preparation of the non-competitive renewal should be specific and emphasize progress towards scientific goals of the original grant application and

progress towards addressing EDRN's mission. While scientific quality and progress need to be recorded and addressed, primarily, metrics should be required to allow NCI staff to report data to NCI leadership.

The review process should assess the progress of each of the funded units towards meeting the specific aims of their funded grant application and their progress and contributions in meeting the above-described charges for the entire group. While the review is structured to provide NCI leadership and staff with data to track the progress of the EDRN and its components, equally important goals are to provide constructive feedback to EDRN Principal Investigators and their collaborators. Reviews may be used by EDRN leadership, NCI staff, and the Network Consulting Team to make mid-course changes or to encourage constructive changes in individual scientific direction or focus. Initial reviews might assist in building collaborations among investigators and their groups. Reviews may also be used to assess administrative progress, to quantify publications and grants, and to quantify numbers of subjects studied.

2. Site Visits

   Each Center/Laboratory should be site visited by a panel comprised of external consultants (including individual members of the Network Consulting Team), NCI staff and other experts on an as needed basis. The site visit should be brief (preferably a half day or less) but enable a thorough review of scientific progress, future scientific plans, performance metrics, facilities and staff in support of the EDRN charge. The site Principal Investigator(s) should provide a 2-3 hour presentation period to review scientific progress, spell out new scientific initiatives for EDRN research, and address required metrics. 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 should be necessary, no scoring should be used.

3. 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 officials will occur in year one, and one mid-grant site visit (for a five-year grant) 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.

4. At time of Type 5 renewal each site must submit their Site Task Reminder list generated from the EDRN Secure Website. In addition each site must submit a copy of each of their individual reports (publications, specimen survey, research interests, and registered protocols).

7.3 Overall Evaluation of Early Detection Research Network

It is the intention of the NCI that the members of the Network Consulting Team and Chairs and Co-Chairs of the EDRN Steering Committee will discuss the overall performance of the EDRN using

the metrics presented in this document and suggest changes/modifications in the working structure of EDRN.

SECTION 8 APPENDICES

8.1 Appendix 1 – Format for Preparing the Last Page of the Application for Use of EDRN Set Aside Funds by Biomarker Developmental Laboratories and Clinical Validation and Epidemiology Centers

It is mandatory that the last page of the application be in the following format:

List separately each collaborating EDRN investigator; specify the specific work they will contribute to the collaboration and where their work will be done (e.g., their laboratory, another laboratory). Also indicate how this work is separate from core work of the investigator already funded by the EDRN; if there is overlap with core funds, please describe the overlap. Note that contributing tissues alone, especially by the CVCs, does not constitute a collaboration with respect to justifying the use of aside funds.

List separately each collaborating non-EDRN investigator; specify their specific contribution to the project and where their work will be done, and how it will be funded.

Describe how this project advances early detection or risk assessment. Also describe how it forwards translational research in general and specifically in areas of diagnosis, prognosis or surrogate endpoints.

8.2 Appendix 2: Format for Application for Developmental Funds by a Biomarker Reference Laboratory

The application for the use of developmental funds should mirror a U01 application with a limit of 25 pages.

The application should focus on the purpose and the mission of the BRLs as described in RFA-CA-14-016. This includes, but is not limited to, analytical validation of published candidate biomarkers; analytical validation of high throughput platforms and methods for efficient, accurate and economical testing of biomarkers using small volumes of samples; pre-validation and validation studies of biomarkers with EDRN BDLs and CVCs; analytical validation of platforms and methods in support of EDRN BDLs and CVCs; development of standard operating procedures, as directed by the EDRN steering committee or by the EDRN executive committee. The BRL may also conduct studies to improve collection, processing and storage of samples and sample sets. Finally, collaboration between BRLs and other EDRN components are encouraged. It is recognized that developmental funds may be used to support several small projects.

The application should be organized in similar manner to traditional grant applications and include, background; hypothesis (if applicable) and specific aims, progress made and or preliminary data; study design, alternative approaches, and methods; timeline and millstones. The last page should follow the format used in the application for set aside funds.

It is mandatory that the last page of the application be in the following format:

List separately each collaborating EDRN investigator, specify the specific work they will contribute to the collaboration and where their work will be done; (e.g., their laboratory, another laboratory). Also indicate how this work is separate from core work of the investigator already funded by the EDRN; if there is overlap with core funds, please describe the overlap. Note that contributing tissues alone, especially by the CVCs, does not constitute a collaboration with respect to justifying the use of aside funds.

List separately each collaborating non-EDRN investigator; specify their specific contribution to the project and where their work will be done, and how it will be funded.

Describe how this project advances early detection or risk assessment. Also describe how it forwards translational research in general and specifically in areas of diagnosis, prognosis or surrogate endpoints.

8.3 Appendix 3 – Guidelines for Reviewing Requests for Release of Set-aside Funds

1. EDRN PI sends request to the appropriate NCI Program Director (PD) within 90 days of award date. PD checks application of completeness. If incomplete, PD requests additional information from the PI. Applications received in the first week of the month should be reviewed during that month's EDRN EC call.
2. PD identifies an EDRN PI, who is not on the EDRN EC, to provide a written review prior to the EDRN EC call. If EDRN PIs lack the necessary expertise, an Associate Member or Co-PI can be used as the reviewer. PD sends the application and review guidelines at least two weeks prior to EDRN EC call.
3. PD assigns two EC members as primary and secondary reviewers for each application. Applications should be sent directly to the assigned EC members two weeks before the EC call. Request that written comments be provided prior to the call. Coordinate EC and non- -EC assignments with other PD to distribute the review workload evenly. A spreadsheet works well for this.
4. During the EC call, the PD introduces the request, briefly describing the specific aims, approach, and collaborators. This should only take 2 or 3 minutes. Both EC reviewers provide their comments. PD presents the outside reviewers comments and if necessary his/her own comments. Open discussion of the application by whole EC. Chair of EC asks for recommendations and EC votes. Possible recommendations:

    - Approve
    - Conditionally approve - PI must revise and/or respond in writing to EC questions and concerns. NCI staff evaluates the response and makes decision about release of set aside funds.
    - Revise- PI must revise and resubmit the request which will be reevaluated by the EC.
    - Disapprove - PI may submit a new set-aside request but it must be for a different project.
5. If the request is not approved by the EC, the PD communicates the result to the PI, providing the written comments of all the reviewers, and if appropriate, a list of questions the EC would like addressed. Depending on the recommendation of the EC, the PI sends a written response, a revised application, or a new application to the PD.
6. Once the request has been approved either by the EC or by NCI staff after an appropriate response, PD writes a letter to the PI informing him/her that the EC recommended approval of the release of the restricted, set-aside funds and advising them that the official notification of the release of restricted funds will come via a revised Notice of Grant Award issued by the NCI Office of Grants Administration.
7. PD sends a memo to the appropriate grants specialist in OGA and to the person in OGA who coordinates the EDRN informing them that NCI program staff recommends the release of the restricted set-aside funds and stating the total costs to be released. The PD also sends a copy of the letter sent to the PI and a signed copy of the application. Send a copy of the memo to the program specialist.

8. PD retains a copy of these communications in their records.

8.4 Appendix 4 – Guidelines for Reviewing Applications for Core Funds

Core Funds are used to support three types of activities - Associate Members, prevalidation or PRIDE studies, and validation trials. These guidelines are for the process of reviewing prevalidation or PRIDE studies and validation trials. The process for reviewing Associate Membership applications is different and is described elsewhere.

According to the EDRN Manual of Operations, applications for Core Funds are accepted the first week of each month and are reviewed during monthly EC calls held the last week of the month.

Reviewing prevalidation and PRIDE applications: (note guidelines for validation studies differ and are given in the next section)

1. The investigator sends the application directly to the NCI Program Director (PD) or to either the chair of the Collaborative Group (CG) or Chair of the EC who will then send it to the appropriate PD.
2. PD checks application to ensure that it complies with the EDRN requirements as specified in the EDRN Manual of Operations. If the application is not compliant, the PD returns it to the investigator for revision.
3. If the application is compliant, the PD sends the application, review guidelines, and the conflict of interest, confidentiality and non-disclosure form to the EDRN PIs who are members of the appropriate CG. The PIs should send reviews back to the PD within two weeks.

   Alternatively, the application for a prevalidation may be sent directly to the EC for evaluation. This decision is based on the size and scope of the application and the PD should discuss this with Sudhir Srivastava. The EC can either proceed as in step 5 or send to the appropriate CG for review.
4. If there is a strong consensus, the outcome of the review (summary of all of the individual comments), the CG's recommendation, and the application are sent to the EDRN EC for discussion at the next conference call.

   If there is no consensus or if the Chair of the CG thinks it necessary, the PD will set up a conference call with the PIs to discuss the application. The application and outcome of the review (summary of all of the individual comments) and conclusion of the conference call are sent to EDRN EC for discussion at the next conference call. The CG may send the application back to the investigator for minor revisions prior to going to EC.
5. During the EC call, the PD introduces the application, briefly describing the specific aims, approach, and collaborators. The Chair of the CG and the PD then summarize the outcome of the review and their recommendations. Open discussion of the application by whole EC. Chair of EC asks for recommendations and EC votes. Possible recommendations:

   - Approve – recommend any changes to budget
   - Conditionally approve - PI must revise and/or respond in writing to CG and EC questions and concerns. NCI staff (assigned PD and other CBRG PDs) evaluates

the response and makes decision whether to fund. If PD cannot decide, consult Chair of CG and if necessary resend to CG or EC for re-review.

- Revise - PI must revise and resubmit the request which will be reevaluated by the CG and EC.

- Disapprove

6. After the EC makes it recommendations, the PD communicates the results to the investigator in writing.

    - If approved, PD sends written comments and any recommended changes to budgets to the investigator. PI may need to submit a revised budget before PD approves funding.

    - If conditionally approved, PDs sends written comments and results of EC discussion to the investigator. PI must revise and/or respond in writing to CG and EC questions and concerns. NCI staff (assigned PD and other CBRG PDs) evaluates the response and makes decision whether to fund. If PD cannot decide, consult Chair of CG and if necessary resend to CG or EC for re-review.

    - If the EC requests a revised application, PDs sends written comments and results of EC discussion to the investigator. PI must revise and resubmit the request which will be reevaluated by the CG and EC.

    - If the EC disapproves, the PD sends the sends written comments and results of EC discussion to the investigator. The PD must edit the written comments such that they accurately reflect the EC discussion.

7. Once the request has been approved either by the EC or by NCI staff after an appropriate response, PD writes a letter to the PI informing him/her that the EC and NCI staff have recommend funding the application. This letter should contain an explanation about the funding mechanism and who will be contacting their business office. The program specialist (currently Felicia Evans Long) will provide a sample letter.
8. PD gives completed and signed application to the program specialist (currently Felicia Evans Long) to send to NCI if current EDRN member or to Fred Hutchinson Cancer Research Center if non-EDRN member for funding. These awards are subcontracts to the grant of the EDRN DMCC (currently Ziding Feng Ph.D.).
9. PD retains a copy of the application, the reviews and all communications.

Reviewing applications for validation trials

Due to the importance of a validation trial, larger costs, more complex organization, and significant involvement of the EDRN DMCC and NCI staff, the application process has some additional requirements. It is a two-step process – a short 3 5page preproposal that is evaluated by the same process as used for prevalidation and pride proposals and a full proposal. The content and requirements for both the proposal and full proposal are given in the EDRN Manual of Operations.

A full validation proposal can only be submitted if the preproposal has been approved the EDRN EC.

1. The investigator sends the full proposal to the PD who then checks to make sure that it follows the guidelines as given in Manual of Operations. There are specific requirement about the involvement of the DMCC, EDRN BRLs and CEVCCVCs
2. If the proposal is compliant, the PD identifies two experts who are not part of the EDRN to provide a written review of the proposal. The PD sends the application, review guidelines, and the conflict of interest, confidentiality and non-disclosure form to these external reviewers at least two weeks prior to EDRN EC call. The reviews of the external reviewers must be sent to the EC at least three days prior to the EC call.
3. PD also sends the full proposal to the EDRN EC at least two weeks prior to EDRN EC call. The PD should assign three EC members to be primary reviewers. The EC may decide to have an ad hoc committee composed of other EDRN PIs also review the proposal. If this decision is made, it is the responsibility of the PD to administer the review by this committee. The review should be run as described above for prevalidation proposals reviewed by the CGs.
4. During the EC call, the PD introduces the proposal, briefly describing the specific aims, approach, and collaborators. The assigned EC reviewers provide their comments, and if there was an ad hoc committee, its recommendation should be presented by a member of that committee or the PD. This is followed by open discussion of the proposal by whole EC. Chair of EC asks for recommendations and EC votes. Possible recommendations:

    - Approve – recommend any changes to budget
    - Conditionally approve - PI must revise and/or respond in writing to CG and EC questions and concerns. NCI staff (assigned PD and other CBRG PDs) evaluates the response and makes decision whether to fund. If PD cannot decide, consult Chair of CG and if necessary resend to EC for re-review.
    - Revise - PI must revise and resubmit the request which will be reevaluated by the EC.
    - Disapprove

5. After the EC makes it recommendations, the PD communicates the results to the investigator in writing.

    - If approved, PD sends written comments and any recommended changes to the budget to the investigator. PI may need to submit a revised budget and work with the DMCC and other components of the EDRN before PD approves funding.
    - If conditionally approved, PD sends written comments and results of EC discussion to the investigator. PI must revise and/or respond in writing to CG and EC questions and concerns. NCI staff (assigned PD and other CBRG PDs) evaluates the response and makes decision whether to fund. If PD cannot decide, consult Chair of CG and if necessary resend to CG or EC for re-review.

- If the EC requests a revised application, PD sends written comments and results of EC discussion to the investigator. PI must revise and resubmit the request which will be reevaluated by the CG and EC.

- If the EC disapproves, the PD sends the sends written comments and results of EC discussion to the investigator. The PD must edit the written comments such that they accurately reflect the EC discussion.

6. Once the request has been approved either by the EC or by NCI staff after an appropriate response, PD writes a letter to the PI informing him/her that the EC and NCI staff have recommend funding the application. This letter should contain an explanation about the funding mechanism and who will be contacting their business office. The precise funding mechanism will depend on how the validation study is organized. There may be a single primary contract from Hopkins to the PI's university with subcontracts to the other participating sites or there maybe individual contracts from Hopkins to each site. The PD must work with the program specialist and the PI of the validation study to work out the details.
7. PD gives completed and signed application to the program specialist (currently Felicia Evans Long y) to send to NCI if current EDRN member or to Fred Hutchinson Cancer Research Center if non-EDRN member for funding. These awards are subcontracts to the grant of the EDRN DMCC (currently Ziding Feng, Ph.D.).
8. PD retains a copy of the application, the reviews and all communications.

8.5 Appendix 5 – Policy on Blinding Specimens for EDRN Collaborative Studies

Definition of blinding:

Any information associated with the specimens remains unknown to the blinded party. Usually the blinded party is only given the labels (coded numbers) associated with the specimens. Some assays requires that cases and controls specimens are allocated with a certain ratio within the assay device. In that case, the blinded party may know the ratio of the mixing if necessary.

Unblinding may occur after the blinded party has completed the assay, completed the quality check of their data, and submitted data to DMCC, and the study group decided decides that the blinding is no longer necessary. Blinding may continue for other reasons (e.g. the reference set specimens that will be used for more than one study).

Studies using prospectively collected specimens:

Prospective study sites should use VSIMS and use the labels provided by DMCC. The labels provided by DMCC ensure the blinding in the subsequent uses of the specimens.

Studies using existing repository specimens:

1. Principal Investigator and any personnel of in his/her lab should be blinded, regardless of whether the actual assay for the study is conducted at PI lab or at another lab. The lab performing study assays should also be blinded.

2. Sites contributing Specimens should contact the DMCC for blinding guidance prior to sending out specimens to a study PI lab or assay lab, and should only send out the specimens after obtaining a written permission from the DMCC.

3. The study group (including DMCC) will determine whether the specimen contributing site could directly send the specimens directly to assay lab without relabeling. Factors to considers includes, but not restricted to, ratio of cases and controls contributed by this the site, the nature of the study (assay done at an independent labor each lab will perform their candidate marker assays, etc). If the study group decides it is necessary, relabeling will be performed prior to the shipment of specimens to assay labs.

Single Site or Collaborative Studies not Coordinated by the DMCC:

EDRN investigators are encouraged to do as much as blinding when as possible even at the discovery phase. For EDRN network collaborative studies, DMCC will perform blinding. For site specific studies or collaborations between sites, the blinding is done locally but investigators are encouraged to consult DMCC regarding blinding procedures.

8.6 Appendix 6 - Request for Specimen Reference Sets

Early Detection Research Network

Part 1: Request For Specimen Reference Sets

Date of Submission:

Investigator: Name: Institution: Address:	 Phone: Fax: E-mail

Specimen Reference Set(s) Requested

Collaborative Group Oversight	Organ Site	Specimen Type
☐ Breast & Gynecological ☐ Colorectal & Other GI ☐ Lung & Upper Aerodigestive ☐ Prostate & Other Urologic	_____ (e.g. lung, ovary, colon, etc)	☐ Serum ☐ Plasma ☐ Other: Specify _____

Minimum volume of each sample required: (microliters)	Expected Length of Study: months

Institutional Approval

Do you have IRB approval to work with the requested samples?	☐ Yes: Institution: Approval Number: ☐ No ☐ Pending: Expected Date:

Funding

How will testing of the reference set(s) be funded?	☐ Current NIH-funded grant: Grant No. Annual Direct Costs: Funding Period: ☐ Other Sponsorship: Please provide a letter of commitment from the sponsoring agency, company, or foundation. ☐ Other: Specify:

Part II: Scientific Proposal

Using the standard PHS 398 Continuation Page (http://grants.nih.gov/grants/funding/phs398/continuation.doc) address the following items as outlined. (3-5 pages recommended)

I. **Clinical Relationship**: Clearly state the clinical question that you are trying to address: risk assessment, early detection, diagnosis or prognosis. How would the reference samples expedite addressing the intended clinical question?

II. **Background and Significance**: Clearly state the scientific rationale of the proposal for using the requested specimen reference set(s). Describe your biomarker/platform and how you came upon its discovery/development for potential application in cancer detection.

III. **Preliminary Data & Methods:** Provide sufficient information describing how experiments were performed, details on convenience samples used, and presentation of data in terms of specificity, sensitivity, and variance of your measurements. Explicit description of your studies will facilitate review considerations. Figures and other supporting documentation can be appended after your proposal.

IV. **Data Analysis Plan:** Specify whether you will need a training set in addition to a blinded test set. Provide adequate detail concerning how statistical analysis of your data coming from these samples will be performed and a justification that the requested references set(s) is/are large enough to demonstrate the utility of the biomarker. Describe the statistical resources at your disposal. If you require statistical support, EDRN can assist you with this.

V. **Collaboration:** In this section state your willingness to deposit all raw data obtained using the reference set(s) with the EDRN Data Management and Coordinating Center (DMCC). EDRN may compare this data as a reference with other biomarkers applied to the same sets.

VI. **Future Plans**: If the biomarker is found to have promising performance characteristics, the EDRN might be interested in working with you to proceed to Phase II clinical validations. Address each specific scenario below according to your intentions:

a. Do you plan to approach EDRN for funding and collaboration in proceeding to a Phase II validation study? If not, do you have other resources where validation can be accomplished? Describe clearly other resources at your disposal and how they are sufficient to complete a larger Phase II validation study if you will not seek help from the EDRN.
b. Are you amenable to working within the collaborative framework of EDRN in proceeding to Phase II studies?
c. If deemed beneficial, will you be amenable to including your biomarker into a larger panel of biomarkers for Phase II validation?
d. If refinements will improve the performance of the biomarker test, will you concur with further development of the test? Will it be advantageous to include resources of EDRN for this purpose?

8.7 Appendix 7 – EDRN Pre/Validation Reference Set Specimen Sharing Guidelines

It is the goal of specimen reference sets to promote the aims of the Early Detection Research Network, i.e., testing and implementation of biomarkers useful for the detection of solid malignancies for the purpose of down-staging incident cancers in the population. Much of the biomarker work to date has been performed on convenience samples from cases and controls. Since these samples have been collected in a variety of ways, comparisons have been difficult. Further, cases and controls may not have been selected and matched using appropriate rigor to reduce bias. Finally, since there has not been a common resource with sufficient amounts of sample, comparison or integration of multiple markers has not been feasible. With the creation of shared and common sets of specimens from well characterized and matched cases and controls from specific disease spectra, the EDRN will overcome many of the logistic and design issues in preliminary and advanced biomarker validation. This resource will be accessible to any investigator within or outside of the EDRN based upon a common and transparent set of criteria used to evaluate applications. It is anticipated that results from these studies will be made publicly available.

The Specimen Resource Sharing Committee was created within the EDRN to draft a process through which these specimen reference sets could be accessed. It is the opinion of this committee that no completely common set of criteria could be used to evaluate biomarkers from the disparate cancers encompassed by these sets. Each cancer site has its own particular requirements, barriers, and opportunities for detection. Therefore, the appropriate organ-specific Collaborative Group should handle the detailed scientific evaluation of applications for samples. However, it was also recognized that certain common guidelines and procedures could be developed and implemented without reducing the scientific and programmatic input of the Collaborative Groups. After providing specific details related to the specimen reference set(s) being requested and institutional approval to use these sets, the investigator is then expected to address the following topics as provided on the application form in relation to his/her biomarker and future intentions:

- Clinical Relationship
- Background and Significance
- Preliminary Data & Methods
- Data Analysis Plan
- Collaboration
- Future Plans

If additional review criteria or application queries for any specimen reference set are stipulated by the corresponding Collaborative Group, the appropriate NCI Program Director will provide this additional material to the investigator. In essence, each Collaborative Group will determine the stringencies for granting access to specimen reference sets they have oversight of. These standards should be established by the Collaborative Groups before the set(s) become available. For each review conducted, it is expected that every Collaborative Group will include an adequate biostatistical critique, either from within a participating laboratory of the Collaborative Group, or by involvement of the DMCC, to ensure that appropriate consideration is given to statistical concerns of the proposal.

Upon receiving an inquiry or request regarding access to specimen reference set(s) the appropriate NCI Program Director will be notified to send an application form and any other relevant documents to the investigator. After the completed application has been returned, the Program

Director will then forward it to the respective Collaborative Group. The Collaborative Group, in a timely manner (within one month) will review and discuss the application and offer a recommendation of whether 1) the investigator should be sent the requested specimen reference set(s), 2) further clarification or revision are needed, or 3) the request is deemed to be of low priority and deferred or denied.

1) If approval is given, the EDRN Executive Committee will be notified at its next monthly meeting by the Collaborative Group chair (or co-chair). If extenuating circumstances require a more timely response, the Executive Committee will be notified by email of this decision and the Committee must respond to the Collaborative Group chair within 48 hours if they have any concerns. As the Executive Committee provides oversight for global EDRN activities, it needs to be informed of requests for specimen reference sets that have been received and reviewed within EDRN. In principle, the Executive Committee will concur with all approvals recommended by Collaborative Groups unless special issues are raised. NCI Program Staff will then notify the facility in Frederick to prepare the materials needed for sending the appropriate specimen reference set(s).
2) If further clarification is needed, the Collaborative Group will inform the Program Director of what concerns or questions remain with the application. The Program Director will then communicate with the investigator of these issues to ask for a resubmission.
3) If deferral or denial is made, the Collaborative Group will provide the rationale to the Program Director why the request was turned down. The Program Director will then relay this decision and its reasons to the investigator.

8.8 Appendix 8 – Policy on Use of VSIMS for EDRN Network Approved Collaborative Studies

Studies using prospectively collected specimens:

Prospective study sites should use VSIMS and use the labels provided by DMCC. The labels provided by DMCC ensure the blinding in the subsequent use of the specimens. The use of VSIMS means that all clinical and epidemiological data pertaining to a specimen be key-entered into the data entry tool, as well as all information about collection, processing and shipping of specimens. Using VSIMS for prospective studies enables the DMCC to query data for accrual, accuracy and eligibility at any time. When sites collecting specimens prospectively continue to use their existing data systems the work involved in exporting and mapping data from the site to the DMCC is extensive. In addition, several of the sites that need to export data to the DMCC do not have the staffing or experience to conduct this request in a timely fashion.

8.9 Appendix 9 – Secure Website Users Guide (separate document)