Crohn's & Colitis Foundation of America

OPERATIONS MANUAL

of the

Pediatric Network

(A Consortium)

I certify this Operations Manual of the Pediatric Network Consortium ("Network") is a valid, authorized document containing policies and procedures for the management of the Network.

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Chair Pediatric Network Committee	Vice President, Research & Scientific Programs
Emory University	Crohn's & Colitis Foundation of America
Date: _____	Date: _____

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General Information:

Background

Children with Crohn's disease show a wide variation in disease activity; some may have mild activity while others have severe disease activity which can lead to poor quality of life, complications and surgery. At this time there are no reliable indicators to predict a more complicated disease course in children first diagnosed with Crohn's disease. This information would be extremely valuable to appropriately tailor more aggressive therapy to children who have a high likelihood of a severe disease course. Currently available therapies alleviate symptoms from the disease, but it is not clear whether any of these treatments modify the natural history of Crohn's disease, and at what time in the progression of disease their introduction would be optimal. The overall goal of this project is to determine clinical parameters and biomarkers that predict progression of disease to the need for surgery as a first step in elucidating these important questions. We will identify factors that mitigate or accelerate disease progression and develop and validate a risk model for predicting severe disease course using state of the art clinical, immune, genetic and bacteriological risk markers in children with newly diagnosed Crohn's disease.

Data to build a clinical prediction tool to the development of structuring/penetrating Crohn's disease will be obtained in a prospective fashion by a large-scale multi-center collaborative effort. To this end, a Pediatric IBD Research Network has been developed under the auspices of the Crohn's & Colitis Foundation of America which involves a structure under which various institutions will work together on mutually agreed upon multiple projects. This new structure will include CCFA representatives, Network investigators, and an external advisory board that will help steer the initial steps of the network's formation and monitor network activities moving forward.

This project will use uniform disease phenotype definitions and an integrated approach for the collection of clinical information, specimen gathering and banking, and storage of data. It is our hope that the analysis of this information will allow us to develop effective tools for disease prognostication, improved therapeutic intervention strategies, and to develop new classes of therapeutics and preventatives.

Definitions

Crohn's disease - Crohn's disease is a chronic (ongoing) disorder that causes inflammation of the digestive or gastrointestinal (GI) tract. Although it can involve any area of the GI tract from the mouth to the anus, it most commonly affects the small intestine and/or colon.

The disease is named after Dr. Burrill B. Crohn. In 1932, Dr. Crohn and two colleagues, Dr. Leon Ginzburg and Dr. Gordon D. Oppenheimer, published a landmark paper describing the features of what is known today as Crohn's disease. Crohn's and a related disease, ulcerative colitis, are the two main disease categories that belong to a larger group of illnesses called inflammatory bowel disease (IBD).

Because the symptoms of these two illnesses are so similar, it is sometimes difficult to establish the diagnosis definitively. In fact, approximately 10 percent of colitis cases are unable to be pinpointed as either ulcerative colitis or Crohn's disease and are called indeterminate colitis.

Both illnesses do have one strong feature in common. They are marked by an abnormal response by the body's immune system. The immune system is composed of various cells and proteins. Normally, these protect the body from infection. In people with Crohn's disease, however, the immune system reacts inappropriately. Researchers believe that the immune system mistakes microbes, such as bacteria that are normally found in the intestines, for foreign or invading substances, and launches an attack. In the process, the body sends white blood cells into the lining of the intestines, where they produce chronic inflammation. These cells then generate harmful products that ultimately lead to ulcerations and bowel injury. When this happens, the patient experiences the symptoms of IBD.

Although Crohn's disease most commonly affects the end of the small intestine (the ileum) and the beginning of the large intestine (the colon), it may involve any part of the GI tract. In ulcerative colitis, on the other hand, the GI involvement is limited to the colon. In Crohn's disease, all layers of the intestine may be involved, and there can be normal healthy bowel in between patches of diseased bowel. In contrast, ulcerative colitis affects only the superficial layers (the mucosa) of the colon in a more even and continuous distribution, which starts at the level of the anus.

CCFA - The Crohn's and Colitis Foundation of America (CCFA) is a non-profit, volunteer-driven organization dedicated to finding the cure for Crohn's disease and ulcerative colitis. It was founded in 1967 by Irwin M. and Suzanne Rosenthal, William D. and Shelby Modell, and Henry D. Janowitz, M.D.

Four decades ago, the Crohn's & Colitis Foundation created the field of Crohn's disease and ulcerative colitis research. Today, the Foundation funds cutting-edge studies at major medical institutions, nurtures investigators at the early stages of their careers, and finances underdeveloped areas of research. Educational workshops and symposia, together with our scientific journal, *Inflammatory Bowel Diseases*, enable medical professionals to keep pace with this rapidly growing field. No wonder the National Institutes of Health has commended the Foundation for "uniting the research community and strengthening IBD research."

CCFA Pediatric Network (PROKIIDS) - In 2007, the foremost pediatric IBD basic and clinical researchers met with the medical leadership of the Crohn's and Colitis Foundation of America (CCFA) to establish priorities in pediatric science and further pediatric IBD treatment and research. Through collaboration between the pediatric community and CCFA the Pediatric Resource Organization for Kids with Inflammatory Intestinal Diseases (PROKIIDS) was developed. The focus of PROKIIDS is to move the pediatric IBD agenda forward while building worldwide awareness around the seriousness of the issues surrounding our most vulnerable patients. The Pediatric IBD Research Network, which falls under the PROKIDS umbrella, is a collaboration of pediatric IBD centers promoting research, education and services. Currently 29 centers around the nation are working together on research projects.

Pediatric Network - The Pediatric Network, referred to as the "Network," is a consortium of multiple centers working together on multiple research studies. All research studies to be conducted through the Network will be pre-approved by the Steering Committee, and based on study needs. Any number of the centers involved in the consortium may participate.

Pediatric Network Steering Committee - The Pediatric Network Committee is the steering committee for the Network. This committee consists of the Pediatric Network Committee Chair, Co-Chair, Chairpersons of various subcommittees, and participating institutional and affiliate members. The Chairperson of the CCFA National Scientific Advisory Committee (NSAC), the CCFA Vice President of Research and Scientific Programs, Chair of the CCFA Pediatric Affairs Committee, CCFA Chief Medical Advisor and Chair of the Board of Trustees (or designate) shall be members ex-officio of the Pediatric Network without vote. Committee membership will be renewed, and rotated every three years.

Operations Manual - The Operations Manual is the guide for the Network. It defines all aspects of the Network, and how research studies will be conducted within the Network, including operations, requirements, expectations, and policies and procedures.

Clinipace, Inc. – Clinipace, Inc., provides Right-Sized™ clinical research solutions for phase I-IV clinical trials, registries, and investigator-initiated grants management programs conducted by biopharmaceutical and medical device companies and academic medical centers. Clinipace will operate as the Data Coordinating Center for the Network.

Data Coordinating Center (DCC) - The DCC was established as part of the Pediatric Research Network to support the data management and analysis of research data for the network, and to identify opportunities to implement data standards and share resources across the network. The DCC participates in the design of clinical protocols, management of the protocol and amendment approval process, in addition to providing the data management and analysis necessary to support them. They facilitate data entry by building and maintaining data entry forms. The DCC has developed and maintains the "Protocol Manager" clinical data management system used for the collection, storage and

analysis of data for all clinical sites that participate in network studies. They are also responsible for generation of reports and analyzing data for this study.

1. Purpose

The purpose of the Pediatric Network ("Network") is to act as a resource for studies by scientists and clinicians in the pediatric IBD field. The Network is a single overriding structure which encompasses several sections which include a membership, and various types of studies. These studies include research on genetics, immunology, and the effects of inflammation on growth and bone health, and quality improvement studies.

2. Organization

a. Pediatric Network Committee

The Pediatric Network Committee is the steering committee for the Network. This committee consists of the Pediatric Network Committee Chair, Co-Chair, Chairpersons of various subcommittees, and participating institutional and affiliate members. The Chairperson of the CCFA National Scientific Advisory Committee (NSAC), the CCFA Vice President of Research and Scientific Programs, Chair of the CCFA Pediatric Affairs Committee, CCFA Chief Medical Advisor and Chair of the Board of Trustees (or designate) shall be member's ex-officio of the Pediatric Network without vote. Committee membership will be renewed, and rotated every three years with the exception of the Pediatric Network Committee Chair.

The Pediatric Network shall communicate as often as necessary, but at least meet in person once per year. In addition, the Pediatric Network Committee shall meet on the call of the Pediatric Network Committee Chair. Such special meetings shall be convened within 4 weeks of the date of receipt of the request.

b. Pediatric Network Committee Chair's Responsibilities

The Pediatric Network Committee Chair ("Chair") is responsible for overseeing the quality of the scientific activities and operation of the Network, and shall represent the Network in its business with the NSAC of the CCFA. The usual term of office for the Chair will be three years, and the incumbent Chair can be re-elected without limitation to subsequent terms.

Should the position of the Chair be vacated prior to expiration of the usual term of office by resignation, death, incapacity, or for any other reason, then the Pediatric Network Committee Co-Chair shall finish the term of office.

The Chair shall convene and conduct Network meetings, and his/her institution will act as the Administrative Core for the Network during the term of service by the Chair.

The Chair shall be responsible for the finances of the Network. The Chair shall prepare annual operating budgets and submit a report at each regular meeting of the Pediatric Network Committee on the current and projected financial condition of the Network.

The Chair shall evaluate quarterly the actual financial results being achieved by the individual programs and subcommittees of the Network and shall provide reports at each annual meeting of the Network. The Chair shall provide specific fiscal guidelines in the determination of (1) whether a new program or service should be added, or (2) whether an existing one should be expanded, reduced or terminated.

In summary, the Pediatric Network Committee Chair's responsibilities shall include the following:

- Responsible for network day-to-day operations
- Develop an annual budget for the Pediatric Network.
- Receive, monitor and supervise dispersal of all externally received funds; determine (with appropriate input) overhead for Pediatric Network activities; and report regularly to the Pediatric Network Committee regarding the status of such funds. Contributions should be channeled through the institution of the Pediatric Network Committee Chair, as appropriate.

c. Pediatric Network Administrative Core

The institution of the Chair for the Pediatric Network Committee will act as the Administrative Core of the Network during the term of service by the Chair. The Administrative Core will maintain records of activities and decisions by the Chair in the dispensation of responsibilities as outlined in section 1.b. In addition, the Administrative Core will manage documentation for all the individual programs and subcommittees of the Network during the term of service by the Chair. All documentation will also be on file with CCFA.

When a new Chair for the Pediatric Network Committee is elected from a different institution, the institution of the new Chair will assume the duties of the Administrative Core.

3. Pediatric Network Membership

The Network is open to qualified investigators (see “Members of Pediatric Network, Application Process,” for a definition of qualified investigators) conducting IBD research. Institutional members are independently administered primary centers consisting of hospitals, medical centers or research institutes, or a group of such centers which have developed an IBD-related research program approved by the Pediatric Network Committee. Member institutions functioning in different cities shall be eligible for designation as separate member institutions, even if they are part of a single university. However, where member institutions consist of more than one hospital or institute but remain under the administration of one principal investigator (PI), these

hospitals and institutions shall comprise a single member institution. Different departments, such as Medicine, Pediatrics, Surgery, Pathology or Radiology, at a single member institution shall be considered as part of that member institution.

Where an institutional member is comprised of several hospitals or medical centers who have agreed to come under the administration and coordination of the PI, the PI of the program assumes full responsibility for the operation of the Network functions at these hospitals or medical centers. An institution may be admitted to or removed from membership upon a recommendation and approval of the Operating Subcommittee.

Investigators wishing to participate within the consortium should complete an application to the Network. See Application process under Member of Pediatric Network Section.

4. The Data Platform

Clinipace, Inc., is the Data Platform Provider for this study. The data platform is a web based platform that will allow users access through a single website. The platform will be used for all data entry required for the projects in the Network. Clinipace will be responsible for maintaining the database, for ensuring its compliance to all federal and industry standards, and ensuring its authenticity. The Data Platform will be monitored by the Data Subcommittee.

5. Operations Manual

The Operations Manual will be a guide for PIs on the entire Pediatric Network Project. Subsequently, each project will have a study manual that must be abided by each PI participating in the study. The operations manual will be sent to the PI upon gaining network membership.

Committees

1. Pediatric Network Steering Committee

The Pediatric Network Steering Committee (also referred to as the Pediatric Network Committee) has the following members:

Consortium Principal Investigator- Chair
Chairpersons of various Subcommittees
The Chairperson of the CCFA National Scientific Advisory Committee (NSAC)
CCFA Vice President of Research and Scientific Programs,
Chair of the CCFA Pediatric Affairs Committee
CCFA Chief Medical Advisor
Chair of the Board of Trustees (or designate)

With respect to votes on matters decided by the Pediatric Network Steering Committee, each committee member has one vote. If an affiliate of a Pediatric Network Steering Committee member applies, the committee member will be excused from reviewing and voting on that study proposal, similar to NIH peer review policies for avoidance of actual or perceived conflicts of interest. The CCFA supports the operations of the Pediatric Network Steering Committee by arranging Committee conference calls, receiving submitted applications, administering the process for review of submitted applications, writing correspondence for the Committee, and maintaining the lists of studies and allocated/committed samples and the document and correspondence files relating the Committee's activities. The CCFA is the named liaison for each investigator, and the Pediatric Network Committee members in completion of these activities.

2. The Oversight Committee

The Oversight Committee shall consist of non-members of the Pediatric Network. The Oversight Committee shall communicate as often as necessary, and meet in person at least once per year, usually, but not necessarily in association with Pediatric Network meetings. The Oversight Committee shall be responsible for providing monitoring and approval of overall policies and adherence of the Pediatric Network; it shall work with the CCFA Board of Trustees in the areas of policy and budget; it shall have the power to recall the Pediatric Network Chair and revoke institutional membership; it shall receive reports from the various committees; and it shall conduct other business as presented.

3. Subcommittees:

a. Membership Subcommittee

The Membership Subcommittee shall consist of a Chair and Vice Chair appointed by the Pediatric Network Committee Chair with the approval of the CCFA. In addition, there shall be five other members. The members shall serve for three years, and their terms of office shall overlap to provide continuity of subcommittee activities. Each subcommittee member shall have one vote.

The Membership Subcommittee shall review and evaluate applications for membership, and make a recommendation regarding such applications to the Oversight Committee. The Membership Subcommittee shall also evaluate the performance of participating investigators and shall make recommendations to the Oversight Committee regarding membership continuity.

b. Protocol Review Subcommittee

The purposes of the Protocol Review Subcommittee are to provide a framework for creating protocols, and the appropriate peer review for protocols prior to implementation. Investigator initiated protocols will be also be reviewed by this subcommittee. The Chair of the Protocol Review Subcommittee shall be appointed by the Pediatric Network Committee Chair with the approval of the Oversight Committee. Additional members shall be selected on an ad hoc basis by the Oversight Committee Chair and the CCFA.

The Protocol Review Subcommittee shall participate in the planning, implementation and evaluation of studies performed by the Pediatric Network. The Protocol Review Subcommittee provides expert advice to researchers regarding the application of diagnostic and treatment methods and insures that appropriate and state of the art procedures, methods and technology are used in trials as part of the protocol review process. The Subcommittee shall determine whether the investigators proposing Pediatric Network studies have necessary expertise to implement and conduct Pediatric Network approved research.

c. Publications Subcommittee

The purpose of the Publications Subcommittee is to assure, on behalf of Network membership, that archival records in peer-reviewed journals are maintained in a vibrant and healthy state, and to strongly encourage the Network membership to publish in such journals.

Network members should observe the following procedures in submitting publications for review:

1. The Publication Subcommittee should be notified when a publication is initially conceived rather than when it is completed.
2. The Chair will work with the investigator to develop a timetable. Be sure to allow at least two months for the review process, from initial notification to approval.
3. The investigator will provide multiple copies of the proposed publication, sufficient for distribution to each Subcommittee reviewer, as specified by the Chair. Copy must be submitted in final form; preliminary materials will not be considered. Include any additional information that would be useful to the Committee.

4. The review will take place in a scheduled meeting/teleconference of the Subcommittee. Investigator will be teleconferenced into the meeting to answer any questions that might arise.
5. The committee will take one of three actions:
    * Approve the publication as presented
    * Return the publication with suggestions for improvement and a timetable for expedited resubmission
    * Reject the publication on specific grounds
    * An individual institution or individual investigator has the right to publish their own findings despite the disapproval of the steering subcommittee. However, they should acknowledge this disapproval in their manuscript.
6. The Chair will notify the unit in writing of the result of the review within ten (10) days.
7. When approval is received, the investigator may proceed with reproduction and distribution of the publication. Significant changes or alterations to the content or format of the publication subsequent to approval will necessitate resubmission for an additional approval.
8. All published reports, both formal and informal, will acknowledge CCFA support.

d. Data Subcommittee

The Data Subcommittee consists of an external member familiar with data information technology, members of the consortium and a CCFA member. The purpose of the Data Subcommittee is to create, monitor, and revise (as necessary) the Pediatric Network Data platform. The Data platform is hosted by an organization called Clinipace, Inc., and it is up to the Data Subcommittee to ensure that this external group is meeting the needs of CCFA, and the Network.

The Data Committee will review all forms that are written for the Data Platform. They will review workflows and protection rights, and determine whom will have access to what information. They will oversee the use of the quality of the data. Also, should a study require access to the data, the committee will review the protocol, and determine what data is accessible for the study, and in what formats.

Members of Pediatric Network

1. Application Process

The Pediatric Network is open to qualified investigators conducting IBD research. Investigators wishing to participate within the consortium need to apply to the Network. The Membership Subcommittee will review the application based on the following criteria, using the expertise represented by the Subcommittee. If the Subcommittee feels it lacks the expertise to adequately evaluate the merits of an application, they may seek input from external experts:

- Qualifications and interest of the investigator(s): Is the investigator capable of carrying out existing studies in the Network or newly proposed research (refer to the Protocols/Studies section) and maintaining responsibility throughout the duration?
- Burden to the study: Is the patient population willing to participate in study? Do study coordinators have sufficient time to allocate to the study?
- Facility: Does the investigator's location have the capability to collect and ship samples?
- IRB: Does the institution have an IRB? How often do they meet?
- Study Population: Does the investigator have the appropriate patients for which this study is recruiting? Geographically, is he/she in a good area for recruitment? Study sites will be asked to meet pre-determined patient enrollment thresholds as applicable per study.
- Prior record of demonstrated ability to work in collaboration and recruitment of patients in clinical studies

The Pediatric Network Committee has the right to disqualify an investigator based on faulty information on an application, or the lack of a complete application. The Pediatric Network Committee will meet periodically to review all new applications.

2. Requirements of the Site Principal Investigator

Once a site principal investigator (PI) is approved for participating in the Pediatric Network, a contract will be sent to the PI outlining his/her responsibilities. This contract will serve as an agreement between the PI and the Pediatric Network as a subsidiary of the CCFA. Once a signed contract is received, the PI will receive the following items approved for an existing Network study or newly proposed research (as previously provided by the PI with application to join the Network):

- Study Protocol and Draft Consent Forms
- Operations Manual
- Username and Password for Database (provided by DCC-Clinipace)

The PI will be required to submit the protocol and consent forms to their IRB for approvals. Monies for the study operations will not be provided until IRB approvals are sent to the Pediatric Network Committee.

Twice every year, a progress report must be submitted to the Pediatric Network Committee. The report will include:

- Number of Enrolled Patients along with demographic data
- List changes to the facility and its staff
- Budget information
- Results, comments or thoughts observed from the study
- Updated IRB approvals and/or Consent Forms

3. Access to Data Platform

As a member of the Pediatric Network, the PI will have access to the Pediatric Network Data Platform. Once approved for Network membership, the Data Subcommittee will review the PI's application and determine the level of access the institution will need. Clinipace will then be contacted to set up the member and give a tutorial on the data platform.

4. Sample Collection

Depending on the Protocol, Network members may be required to collect biologic samples from their patients. If this is the case, a tool kit will be sent with specific instruction on collection, storage and shipment of the samples. Training will be provided by the Project Manager at the Administrative Core institution.

All samples are stored at the Emory University Repository. Samples in the main Repository are co-owned by CCFA, and the members of the Pediatric Network. The samples will be used by the Pediatric Network for studies that fall within the Network. The Pediatric Network Steering Committee will decide on which studies samples may be used.

A PI will have joint ownership with the Network of all data and samples collected during the PI's participation in the study. Once the study is completed, the PI will maintain joint ownership of the data and samples for thee years after the end of the study to give time for discovery and an exclusivity period whereby materials will not be released for use by PIs not on the study. After the three year time period, samples will be completely de-identified, and ownership will revert to CCFA. Samples WILL NOT be used for commercial gain or to generate money.

If a PI decides to terminate their participation in the Pediatric Network, their rights to samples stored in the primary repository will also be terminated.

Refer also to the section on Regulatory Issues, item 3: "Ownership of Data and Samples."

5. Renewal

Network members must renew eligibility every five years by re-applying to the Network, although there will be no break in membership during the reapplication process. The intent is to confirm the member is still dedicated to the objectives and direction of the Network.

During the renewal period, or at any other time, the Network may elect to terminate a member if found to not be using good clinical practices or if other questionable circumstances exist. The Pediatric Network Steering Committee, Oversight Committee, and Membership Committee will be consulted prior to a member termination. At the time of termination, the member will forsake all rights to any data that they may have collected, and/or samples.

6. Termination

A Network member may choose to terminate membership at any time. At the time of termination, the member will forsake all rights to any data that they may have collected, and/or samples.

If an investigator chooses to quit a study early, or terminates their membership with the Pediatric Network, they must relinquish all rights to the data and samples. The ownership of the samples and data will belong to the Network and CCFA until the study is completed plus 3 additional years. After the 3 year time period, samples will be completely de-identified, and ownership will revert to CCFA. Samples WILL NOT be used for commercial gain or to generate money.

The Pediatric Network Steering Committee may also choose to terminate a member at any time due to the following:

- Lack of study participation and/or results
- Low enrollment or site shows to have poor population for studies
- Identified as not following good clinical practices
- Other reasons as identified by the Steering Committee by majority vote

Protocols/ Studies

Each member of the Pediatric Network must be participating in at least one of the studies that are linked with the network.

1. Application Process

A PI may submit a study for the Pediatric Network by completing a CCFA application. A copy of the research protocol, draft consents, project references, and PI biosketch must be attached to the application.

The Protocol Review Subcommittee will review the protocol based on the following:

- Relevance of study to mission of the Pediatric Network
- Scientific Merit
- Adequacy of study design to address proposed study endpoints
- Assessment of the trial's safety
- Biostatistical design
- Priority of study, if there are competing studies
- Qualification of investigator to perform study
- Possible accrual/projected accrual
- Feasibility of timely completion
- Appropriateness of Data Safety Monitoring Plan or need for a Data Safety Monitoring Board
- Conflict of interest

If approved by the Protocol Review Subcommittee, a recommendation will be forwarded to the Pediatric Network Steering Committee to approve the study for funding. The Pediatric Network Chair will then review the protocol, and along with the Protocol Review Subcommittee, present it to the Pediatric Network Steering Committee for their approval. If approved, then the appropriate NSAC Committee and ultimately the CCFA Board of Trustees will be approached regarding current funding of the study by CCFA. If the board accepts the proposal, along with the projected budget, the study will be approved.

2. Request For Proposal (RFP)

The Protocol Review Subcommittee is in charge of creating a framework for creating new protocols that would fall under the Pediatric Network. Once the Subcommittee decides that a new study is required to fulfill a specific purpose of the Pediatric Network, an RFP will be drafted. The appropriate NSAC Committee and ultimately the CCFA Board of Trustees will be approached regarding the need and funding of the RFP. If approved, the RFP will be sent via e-mail blast, and posted on the CCFA website. Responses will be received and reviewed by the Subcommittee. The process is the same as described in the Protocols/Studies section.

3. Recruiting Sites for New Studies

When a new study is introduced to the Pediatric Network, it will be published in the Pediatric Network Newsletter. Any sites that are members of the network may choose to participate. They will have to apply to the Pediatric Network Steering Committee, and the decision on whether to accept a member to the study will be decided between the Pediatric Network Chair and the study's primary PI.

4. Consent and IRB Issues

Once approved by the Pediatric Network Committee, the consortium will provide the investigator with a copy of the Protocol and draft consent forms. Each site participating must have approval from their IRB for participation in the study. Each site must provide a copy of their initial notice of IRB approval of the study and a copy of their IRB-approved consent to the Committee prior to initiation of study activities. Copies of notices of renewal of IRB approval must also be provided to the Committee annually. The DCC will maintain a file of study IRB approvals and IRB-approved consents, if required.

5. Expiration of Approval/ Progress Report

In general, approved PI's must initiate the study within 1 year of being approved by the Committee, or the approval will be withdrawn. In this case, network resources will be reallocated. The main reason for PI removal from the network will be failure to enroll patients and inability to fulfill contractual responsibilities. The principal investigator will receive written notice 2 months before a study's approval is due to expire. At this time, the PI must submit a progress report with renewal information. Should the PI not meet the expectations of the consortium, his/her membership will not be renewed.

6. Changes to an Approved Study Protocol

If a major change occurs to a study protocol (e.g., addition of a visit, addition of a specimen, something that affects the impact on the participant or resource used), the Pediatric Network Committee will review the changes. Once approved by the Committee, a new version of Protocol along with edited Consent Forms will be sent to participating members. These documents must be reviewed and approved by your IRB, and a copy of all approvals must be provided to the Committee.

Regulatory Issues

1. Confidentiality

Confidentiality of individually identifiable data about study participants must be assured. In addition, any potential collaborators must agree in writing to maintain confidentiality of all data and study information that is not in the public domain, and must agree not to share such data and samples with unauthorized third parties.. All confidential information will be maintained at the Pediatric Network Members site for a period ending five (5) years from the date of their termination from the study. Patients will be re-consented who become 18 years of age (the age of consent) during the time their samples are still being utilized.

2. Disposition of Data and Samples

Data products resulting from studies will be jointly developed by the investigators and the Pediatric Network Committee. These data products will be integrated into the database maintained by the DCC, where they will reside through the end of the study. Also, some data products may be made available to the public domain after the first period of the study ends with the appropriate approval process. All samples will be maintained by the Pediatric Network bank. Exceptions to this policy can be considered on a case-by-case basis by the Pediatric Network Committee.

3. Ownership of Data and Samples

Data and samples collected using the Network central resources are overseen by the Network. CCFA, the Pediatric Network, and PIs co-own data and samples. Data and samples collected from study participants under the study protocol and using study resources are overseen by the Network, PIs and the DCC.

If a discovery is made by a PI who is part of the Network and using the material, the rights of the discovery will belong to the PI and institution, but CCFA must be mentioned in publications.

A PI will have joint ownership with the Network of all data and samples collected during the PI's participation in the study. Once the study is completed, the PI will maintain joint ownership of the data and samples for thee years after the end of the study to give time for discovery and an exclusivity period whereby materials will not be released for use by PIs not on the study. After the three year time period, samples will be completely de-identified, and ownership will revert to CCFA. Samples WILL NOT be used for commercial gain or to generate money.

If a PI chooses to quit a study early, or terminates their membership with the Network, they must relinquish all rights to the data and samples. The ownership of the samples and data will belong to the Network and CCFA until the study is completed plus three additional years. After the three year time period, samples will be completely de-identified, and ownership will revert to CCFA. Samples WILL NOT be used for commercial gain or to generate money.

4. Publications, Abstracts and Presentations

Proposed publications arising from this study must be reviewed by the Publications Subcommittee. The primary purpose of the review is to ensure that any statements about the protocol are accurate and that the resources used in the study are appropriately acknowledged. The acknowledgement will indicate that the results and interpretations are those of the author(s) and do not necessarily represent the opinions of the Study Group. A scientific review will also be conducted. The process for review will be:

- The draft manuscript should target a specific journal and be sent to the Publications Subcommittee.
- The paper will be circulated to the Pediatric Network Steering Committee for voluntary comments directed to the corresponding author.
- The chair of the Publications Subcommittee will identify an internal reviewer for the paper and forward the paper to that individual.
- The reviewer will review the paper for accuracy of statements about the resources used in the study and for appropriate acknowledgment of the Pediatric Network.
- The reviewer will send comments to the chair of the Publications Subcommittee.
- The chair of the Publications Subcommittee will send a written review to the author.

If a manuscript is not accepted upon initial submission to a journal, the manuscript does not need to be re-reviewed by the Subcommittee after revision and prior to resubmission to a journal, unless there have been substantive changes to the statements that relate to resources or the acknowledgment of the Pediatric Network. The Subcommittee Chairperson will decide if re-review is needed.

Abstracts and presentations arising from this study will not require approval from the Network. However, the Network must be informed about such presentations and will provide review of materials if requested. It is expected that any presentation from a study will include appropriate acknowledgment of the Network resources used by the study. Authorship for publications and presentations from the study is at the discretion of the Pediatric Network Committee.