DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK

ORGANIZATIONAL STRUCTURE

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A. Introduction

The permanent central units of the project include the Coordinating Center and the Operations Center.

The committee structure includes an Executive Committee and the Operations Group, as well as two National Eye Institute appointed committees: the Data and Safety Monitoring Committee (DSMC), which is advisory to the Coordinating Center and the National Eye Institute (NEI), and an External Protocol Review Committee, which is advisory to the NEI. Sub-committees will be created by the Executive Committee as necessary.

The Executive Committee is responsible for providing scientific oversight of Network activities, including scientific oversight of both the Operations Center and the Coordinating Center as well as oversight of Network policies within the confines of the NIH terms and conditions for cooperative agreements. The Executive Committee can be considered analogous but not synonymous to a board of directors with respect to making policy decisions that are necessary for the scientific aspects of the Network, providing advice regarding Operations Group activities, selecting the Network Chair (subject to approval of the National Eye Institute) and Vice Chairs, and providing members who serve as part of periodic review of the Coordinating Center and Operations Center. The Operations Group is responsible for implementing the daily scientific operations of the Network and providing recommendations to be approved by the Executive Committee, analogous to senior officers (e.g., chief executive officer, chief operations officer, and other key positions) of a company. The Network investigators serve in an analogous role as "employee shareholders" of the Network, whose participation are needed to implement protocols; for example, implementation of protocols recommended by the Executive Committee and major publications of Network protocol results can occur only with buy-in and enthusiasm of Network clinical sites.

B. Central Units

I. Coordinating Center

The DRCR.net Coordinating Center is located at the Jaeb Center for Health Research in Tampa, Florida. Specific responsibilities of the Coordinating Center include:

- Solicit ideas for new studies from investigators
- Assist the Operations Group with the development of study protocols and the protocol development committees
- Obtain and maintain INDs and IDEs

- Develop study documents such as protocols, operating procedures manuals, and data collection forms
- Maintain version control of all protocols, study documents, publications, presentations, and the like
- Coordinate and monitor the conduct of study protocols
- Develop and implement a data management system capable of supporting multiple projects
- Develop and maintain a multi-functional private website for use by the Coordinating Center, clinical centers, retinal imaging reading centers, Operations Center, and committee members
- Develop and maintain a website for public use
- Develop procedures for patient enrollment and randomization
- Develop and implement a system for adverse event reporting
- Develop and implement a quality assurance program that includes training and certification of clinic staff, monitoring of adherence to the protocol, reporting of quality control data, validation of collected data, assessments of retinal imaging reading center(s), and assessment of drug packaging and labeling
- Coordinate the selection process of clinical centers in conjunction with the Network Chair
- Develop procedures and materials for certification of clinical centers and associated staff
- Develop systems to assist the clinical centers in maintaining a high rate of patient retention
- Develop and maintain a system to facilitate communication between the central units, clinical centers, and committees
- Develop and maintain a system for drug distribution and accountability
- Coordinate site visits, prepare site visit agendas, and prepare site visit reports
- Develop and maintain a system for semiannual collection, review, and reporting of financial disclosures for investigators, coordinators, and other key personnel as defined in the Network's Financial Disclosure policy
- Develop a system, if needed, for integration of a central laboratory into the project
- Develop and oversee implementation of subcontracts with clinical sites to participate in DRCR Network protocols
- Develop contracts with other centralized resource groups utilized in DRCR Network protocols, such as imaging reading centers for grading and transmission of imaging data to the Coordinating Center
- Develops contracts with industry collaborators following the DRCR Network's Industry Collaboration Guidelines
- Develops processes to accept unrestricted gifts within regulations and approval of the National Eye Institute
- Implement subcontracts with the participating clinical centers

- Develop materials for IRB submissions by the clinical centers
- Track IRB approvals and expirations
- Develop study close-out procedures and materials
- Develop statistical analysis plans
- Coordinate the preparation and publication of study manuscripts, including drafting the initial manuscript draft
- Conduct data analyses for Data and Safety Monitoring Committee review as well as for manuscripts, abstracts, presentations, and ancillary studies
- Coordinate activities with the Operations Center, Executive Committee, Operations Group and any other committees
- Coordinate activities of the Data and Safety Monitoring Committee
- Arrange conference calls
- Arrange meetings, including semiannual Protocol Review Committee/Operations Group Quality Control meetings, semiannual Coordinator/Investigator meetings, semiannual Executive Committee/Protocol Prioritization & Planning meetings, semiannual Data and Safety Monitoring Committee meetings, and Protocol Development Committee meetings
- Develop and disseminate agendas and summaries of committee conference calls and meetings in coordination with the Operations Center
- Assist with communication with NIH, JDRF, regulatory agencies, and the public
- Develop clinical center budgets in conjunction with the Executive Committee
- Develop and maintain directory of project personnel
- Maintain direct contact with study participants

II. Network Chair and Operations Center

The Network Chair works closely with, but independently of, the Coordinating Center for the following specific responsibilities:

- Assume overall scientific responsibility and direction for Network protocols
- Chair the Operations Group to manage day-to-day Network scientific activities
- Provide input and assist with preparation of all manuscripts, abstracts, and slide set presentations
- Provide initial review of Network financial disclosures with the PI of the Coordinating Center or senior member of the Coordinating Center designated by the PI to determine if a financial conflict exists per the Network's policies based on disclosures (subject to review and final decision of the Executive Committee) and to recommend plans to manage any financial conflicts (subject to review and final decision of the Executive Committee)
- Serve as spokesperson of the Network to the public

- Chair monthly investigator calls
- Represent the Network with regulatory agencies such as the FDA
- Assist the Coordinating Center with communication with IRBs when ophthalmic expertise is needed
- Assist and back-up Protocol Chairs
- Participate with the Coordinating Center in coordination of activities between the Network and the NEI
- Assist with communication with NIH, JDRF, regulatory agencies, and the public
- Participate and serve as spokesperson in coordination of activities between the Network and industry (for-profit) sponsors, other not-for-profit sponsors (e.g., Juvenile Diabetes Research Foundation, International), and third party payers
- Identify potential funding sources
- Assist the Coordinating Center with oversight of the Network annual budget including determining amounts available for new protocols
- Review and approve new site/investigator Network applications
- Communicate with international sites interested in participating in the Network
- Work with the Coordinating Center to coordinate and back-up the activities of the Vice-Chair(s) and other funded "working" positions (e.g., investigators funded to work on protocol development or manuscripts or presentations)
- Provide support to other researchers desiring to use methodology developed for Network operations or protocols, such as financial disclosure procedures and competing studies procedures
- Review of 'competing studies' proposals, with regard to impact on existing or planned DRCR.net protocols
- Serve as an ex officio representative to the Data and Safety Monitoring Committee and the External Protocol Concept Review Committee as needed
- Oversee consultant expertise when needed for a specific protocol for which expertise is not available within the Network.

The Network Chair will be selected through solicitation of Network participants. The Network Chair will serve no more than two five-year termscoincident with the funding cycle of the DRCR.net Operations Center. (Refer to separate document, Process for Selection of DRCR.net Chair, for more details.)

III. Network Vice-Chair(s)

The Network Vice-Chair(s) will work closely with the Network Chair and Coordinating Center to oversee site monitoring and protocol monitoring, develop and maintain quality assurance, and backup the Network Chair and Protocol Chairs when needed. Each Vice-Chair works with his or

her Coordinating Center Protocol Monitor and is responsible for maintaining communication with their designated sites' investigators to resolve issues, encourage enrollment, and discuss other protocol- or site-related issues. For a complete listing of responsibilities, see Operations Group.

Up to three Network Vice-Chair(s) may serve the Network at any given time. Network Vice-Chairs will be selected through solicitation of Network investigators. Each Network Vice-Chair provides at least 10% effort for Network-related activities. The Vice-Chair(s) will serve one-year renewable terms, up to three years with the exception of the inaugural Vice-chairs. For the inaugural Vice-Chairs, at least one will rotate off after years two, three, and four, so one member will have the opportunity to serve as Vice-Chair for two years and one member for up to four years. (Refer to separate document, Process for Selection of Network Vice-Chair, for more details).

IV. Other Network Investigator Positions(s)

The Network creates other Investigator Positions as needed, for example, for manuscript and protocol development. Investigator members serving in these positions will serve one-year terms renewable throughout each NIH grant period. Members serving in these positions will work closely with the Network Chair and Coordinating Center for new protocol development and implementation and manuscript preparation with the following specific responsibilities:

- Conduct initial review of submitted protocol concepts for discussion with the Operations Group
- Work with the Protocol Chairs, Network Chair, Coordinating Center staff, and Protocol Development Committees on protocol development
- Develop drafts of new protocols
- Review data to be collected for each protocol
- Assist Coordinating Center in developing materials for a protocol, including Procedure Manual, certification materials including Q and A, case report forms (including review of website application, and site budget
- Review of data to be collected in network protocols, including case report forms, imaging (e.g., OCT, photos, FA) and other types of data collection
- Conduct initial review of submitted ancillary study concepts from investigators, research the topic when needed, and decide on degree of merit and priority for recommendation to the Executive Committee
- Work with the Coordinating Center staff to develop and evaluate manuscript proposals
- Work with the Coordinating Center staff to develop, review, refine analyses for the proposals
- Review manuscript outlines, initial data, and manuscript drafts
- Write parts of manuscripts including literature reviews
- Draft responses to journal reviewer comments

- Development of analyses, abstracts, and final presentation materials for meeting presentations
- Provide oversight to meeting presentations
- Assist the Coordinating Center and Operations Group members with manuscript writing/reviewing

C. Clinical Sites

The clinical sites will be responsible for carrying out the common study protocols. A participating clinical site must have at least one individual who meets criteria to be a Network Investigator (refer to a separate document, DRCR Site Requirements, for additional information). One investigator at the site must be designated as the principal investigator, who will have overall responsibility for all study-related activities and all data collection at the center (refer to a separate document, Responsibilities of DRCR.net Principal Investigators for Research Data Integrity, for additional information). Additional clinical site staff include co-investigators, clinic coordinators, and other personnel as needed for the project. Appropriate backup must be available for all positions. Clinical site investigators will have an active role in all aspects of the project including protocol development, data analyses, and publication of results.

D. Protocol Chairs and Protocol Development Committees

Each protocol, including primary protocols and ancillary studies, will have a designated Protocol Chair or co-Chairs. Multi-phase protocols may have a separate protocol chair for each phase. Each Chair will be proposed by the Operations Group and approved by the Executive Committee.

The Protocol Chair's role will focus on scientific aspects of a protocol. During protocol development, the Protocol Chair will work with Coordinating Center staff to develop the protocol.

The responsibilities of the Protocol Chair include, but are not limited to:

- Conduct protocol review calls with investigators at the commencement of a protocol
- Lead in and encourage enrollment
- Respond to protocol queries received from clinical sites
- Respond to protocol treatment deviations by clinical sites
- Consider modifications to the protocol, as necessary
- In general chair writing committee for the primary manuscript from the study
- Provide initial public presentation of main outcomes of the study

Quality control aspects will largely be the responsibility of the Operations Group, as they are generally cross-protocol issues.

In general, an investigator should not serve as Protocol Chair for more than one major project at a time.

A Protocol Development Committee will be formed for each protocol. This will include the Protocol Chair, representatives of the Coordinating Center and, when appropriate, reading center or other resource sites, the Network Chair, and other selected investigators and coordinators. The activities of the Protocol Development Committees will be coordinated by the Coordinating Center.

The responsibilities of the Protocol Development Committee include, but are not limited to:

- Development of the final protocol, informed consent form, data forms, study procedures, and other study materials
- Development of certification requirements for site personnel
- Pilot testing of study forms and procedures prior to commencement of study participant recruitment

Some protocols in development may require specialists from outside of the Network where additional expertise is needed. The Operations Group will select specialists for such protocols. The specialists will join the designated Protocol Development Committee(s) and will focus on the non-retinal scientific aspects of the protocol(s).

E. Committees

I. Executive Committee

The standing members of the Executive Committee will include all members of the Operations Group (listed in a separate section), each Protocol Chair, an NEI representative, a Reading Center representative, a rotating site coordinator, and other Network investigators serving in relevant positions, such as the Protocol Development investigator member. Up to two additional rotating site investigators (not Protocol Chairs and not members of the Operations Group), may be selected to join the Executive Committee. An investigator or coordinator from a site on probation is not eligible for nomination to the Executive Committee. If a site is placed on probation, any investigators or coordinators serving on the Executive Committee may be asked to resign. The two site investigators and the site coordinator will be recommended by the Operations Group to the Executive Committee for approval.

In general, Protocol Chairs will serve on the Executive Committee while their respective protocol is active[1]. Protocol Chairs generally will rotate off of the Executive Committee the month after the final study visit of their respective protocol is completed, as recommended by the Operations Group and approved by the Executive Committee. Depending upon the size of the Executive Committee (i.e.; the number of Protocol Chairs), rotating site investigators may serve a one-year term renewable up to two years. If multiple Protocol Chairs are serving on the Executive Committee, then the rotating investigator members' one-year term will not be renewed. If there are not enough Protocol Chairs, the rotating members' one-year term may be renewed for an additional year. The site coordinator may serve a one-year term renewable up to two years. The size of the Executive Committee should not exceed 20 members.

[1] A protocol is considered active until the final study visit has been completed.

One of the Protocol Chairs or site investigators not serving as a member of the Operations Group will serve as the Chair of the Executive Committee for a one-year term. The individual serving as Chair may remain as an ad hoc investigator member on the Executive Committee for one additional year following the end of the Chair term year. The Executive Committee Chair will be proposed by the Operations Group and approved by the Executive Committee. The selected individual should already serve on the Executive Committee the year prior. The Executive Committee Chair will be responsible for leading the monthly Executive Committee calls and will work closely with the Network Chair relating to Operations Group decisions or discussions that need to be discussed with the Executive Committee. Additional responsibilities may be added as needed.

For issues requiring a vote, the Principal Investigator of the Coordinating Center will share a single vote with any co-investigators of the Coordinating Center.

The Executive Committee has overall responsibility for providing scientific oversight of the activities of the project. This Committee also formulates all policy decisions related to the maintenance and conduct of the project.

Responsibilities of the Executive Committee include:

- Primary responsibility for the scientific oversight of the Network
- Provide input on issues related to the Network, including issues brought to the Committee by the Operations Group
- Review monthly recruitment reports on active protocols across sites
- Develop and enforce Network policies
- Develop requirements for the participation of clinical sites and investigators and other site personnel
- Select and prioritize protocols to be developed following recommendation of the Operations Group and buy-in from investigators
- Select Network Chairs and Vice-Chair(s)
- Provide representatives to provide *ad hoc* review of the Coordinating Center and Network Chair's Office. External members of such a review may be included.
- Select Protocol Chairs following recommendation of the Operations Group
- Review recommendations of the Operations Group of imaging needs and reading center(s) for each protocol
- Review progress of imaging reading centers
- Review and approve final protocol and budget
- Consider and approve changes or modifications in protocol as may be necessary or desirable
- Advise and assist the Coordinating Center on operational matters

- Approve protocol dissemination plans including primary outcome manuscripts and presentations
- Approve primary outcome and secondary outcome manuscripts
- Review and approve ancillary studies as recommended by the Operations Group
- Review and approve collaborations and funding, including unrestricted grants or gifts from Industry or foundations
- Provide input to the Coordinating Center and Operations Center on Network budgets

The Executive Committee will convene by conference call once per month. Additional calls will be held as needed. In general, two in-person Executive Committee meetings will be held each year. Additional individuals (e.g., Protocol Chairs) may be asked to participate as indicated, which may require pre-approval by the Executive Committee Chair.

II. Steering Committees and Other Subcommittees

Steering Committees and other subcommittees may be developed as needed for non-Network areas where additional expertise is desired (e.g. genetics studies).

III. Operations Group

The Operations Group includes the current and past Network Chair(s), the Network Vice-Chair(s), an NEI representative, and the Coordinating Center Principal Investigator and Executive Director.
Specific functions of the Operations Group include:

Develop and maintain a program of quality assurance in the study

- Monitor the performance of all participating sites and central units
- Each site will be assigned to a team consisting of a Coordinating Center protocol monitor and a Vice-Chair investigator who will be responsible for oversight of that site's performance, including recruitment.
- Review quality assurance reports regarding Network performance, comprehensively on a semiannual basis, and at any other times that issues arise
- Monitor adherence to protocols through review of collected data regarding performance and site visits (accompanied by outside, independent, unconflicted consultants as needed)
- Review quality metrics across all sites and DRCRnet studies approximately twice per year at in-person meetings
- Review site visit reports
- Report site performance to the Executive Committee as needed

Protocol development

- Review and approve study procedures of new protocols

- Conduct initial review of submitted protocol concepts from investigators and decide on degree of merit and public health importance for presentation to investigators at the semiannual Coordinator/Investigator meetings and recommendation to the Executive Committee
- Select a Protocol Development Committee, if indicated, for each protocol to be developed
- Address imaging issues for Network protocols
- Submit recommendations to Executive Committee

Oversight of active protocols

- Provide input on protocol close-out procedures

Manuscripts

- Conduct initial review of manuscript ideas (with Manuscript Investigator Position) submitted by investigators and decide on degree of merit for recommendation to the Coordinating Center
- Prioritize manuscripts to be written, including review of manuscript ideas solicited from investigators
- Select a writing committee for each manuscript

Presentations

- Plan for meeting presentations
- Review and approve abstracts prior to submission
- Review of posters and presentations

Dissemination of study results

- Develop plan for dissemination of study results as indicated

New centers and investigators

- Communicate with new centers, both before and after Network approval is granted

A weekly conference call of the Operations Group will be held. Additional calls will be held with some or all of the Operations Group as deemed necessary by the Network Chair and Coordinating Center Principal Investigator or Co-Investigator. In general, two in-person Operations Group meetings will be held each year to review quality control, site monitoring, and protocol ideas.

IV. Manuscript Writing Committees

The Operations Group is responsible for the selection of a writing committee for each manuscript. The Operations Group provides oversight of manuscript writing, and at least one member of the Operations Group will serve on the writing committee for each manuscript. In general, each manuscript writing committee will consist of a lead author (or authors, if applicable; for primary manuscripts, this is usually the protocol chair), a lead statistician, an Operations Group member to provide oversight, and additional study group members (investigators and coordinators) nominated by the Operations Group and based upon study recruitment levels or particular expertise in the topic area of interest.

V. Data and Safety Monitoring Committee (DSMC)

The responsibility for reviewing the ethical conduct of the study and for monitoring the data for evidence of adverse or beneficial treatment effects is assigned to the Data and Safety Monitoring Committee (DSMC). The Data and Safety Monitoring Committee is advisory to the Coordinating Center.

The members of the DSMC will be selected by the National Eye Institute, which will select one of the members to serve as the Chair. The members will include individuals with expertise in clinical trials, biostatistics, diabetic retinopathy, and diabetes as well as a layperson. The NEI Project Officer will be considered an ex-officio nonvoting member.

Prior to the initiation of recruitment for a protocol, the DSMC must approve the study protocol, including the informed consent procedure and form. Subsequent protocol changes that are substantive must be approved by the DSMC prior to implementation. Minor changes that do not impact patient safety or the assessment of efficacy do not require prior DSMC approval and will be reported to the DSMC at its semi-annual meetings. At its discretion, the DSMC may recommend to the Executive Committee that a protocol change be considered.

The DSMC will periodically review the progress of each protocol involving patient safety (at least twice each year either at a meeting or via a conference call) and any other protocol they deem would benefit from their monitoring. In conjunction with the Coordinating Center, the Committee will determine specific plans for evaluating adverse effects and efficacy, including deciding whether a formal interim analysis should be performed.

Recommendations made by this Committee relating to the protection of patient rights and/or resulting from data analyses are forwarded to the National Eye Institute. For randomized clinical trials, results are not available to the participating investigators involved in patient care until the DSMC recommends that this information be released.

DSMC financial disclosures will be reviewed by two individuals with experience in financial disclosures and financial conflicts who are independent of the Operations Center and Coordinating Center investigators. These two individuals will provide advice to the Network Chair and PI of the Coordinating Center or designate regarding financial conflicts and management of financial conflicts following Network policies. It is anticipated that this external advice usually or always will be followed. This external advice will be documented along with any rationale if and when the advice is not followed.

Further details of the role of the DSMC appear in the DSMC Standard Operating Procedures.

DRCR.net Organizational Structure