DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK

POLICIES (Version 7.0)

1. Organizational Structure

The DRCR.net is a structured organization with two permanent central units: the Coordinating Center and the Operations Center. The structure of the Network also includes an Executive Committee, Operations Group, Data and Safety Monitoring Committee, and an External Protocol Review Committee. Additional sub-committees such as Protocol Development Committees and Manuscript Writing Groups are developed as needed. The central units and committees are responsible for carrying out specific tasks as outlined in the Organizational Structure (Policy Appendix V: DRCR.net Organizational Structure).

2. Editorial Policy

Each protocol conducted by the DRCR.net will be reported in one or more manuscripts. Ownership of the data collected as part of all Network protocols resides with the investigators. Datasets are maintained at the DRCR.net Coordinating Center and released for reporting in publications and presentations according to the policies below. The Network "Sponsor", the National Eye Institute (NEI) of the National Institutes of Health, will be provided an opportunity to review and comment on each manuscript, but will have no authority to restrict publication or presentation of study results. Should the Network become involved with other entities that serve as Co-Sponsors with the NEI, this same policy will be in effect.

All manuscripts to be written and national/international presentations to be made in relation to any aspect of the project including but not limited to study protocols, study results, and study conduct must receive the approval of the Executive Committee. The Executive Committee must approve primary outcome manuscripts, secondary outcome manuscripts, or methodology manuscripts. The topic for a manuscript or presentation may be initiated by the Operations Group, Executive Committee or by any participant who may send a suggestion for a paper (using DRCR.net Manuscript Idea Form) to the Operations Group.

Since every investigator cannot have an active role in writing a paper, a Writing Committee will be established by the Operations Group for each paper. Investigators may volunteer for these writing assignments. Generally, the Protocol Chair will be the lead writer on the Writing Committee of the primary outcome paper. A decision on the authorship listing will be made prior to the writing of each manuscript by the Operations Group. The list may be modified by the Operations Group prior to manuscript submission to account for unanticipated contribution effort of any individual.

The Executive Committee must approve all manuscripts and the Operations Group must approve all abstracts about each study or any ancillary study prior to submission for publication. Abstracts not requiring DSMC approval must be submitted to the Coordinating Center at least three weeks prior to the submission deadline. Abstracts requiring DSMC approval must be submitted to the Coordinating Center at least two months prior to the submission deadline. If data are needed for the abstract that have not been previously compiled and verified by the Coordinating Center, the Coordinating Center must be contacted at least 6 weeks prior to the submission date.

For major manuscripts, the Diabetic Retinopathy Clinical Research Network will be listed as the author on the title page, if this meets with journal approval. The writing committee for the manuscript will be listed. Group authored manuscripts will require Principal Investigator sign-off on behalf of the the clinical site or central unit. All investigators and coordinators who participated in the protocol and had at least one study participant completing the primary outcome visit (1) will be given an opportunity to review and comment on the manuscript, (2) will be listed in the manuscript (if permitted by the journal) and (3) can include the manuscript on their CVs as a co-author. Each manuscript will acknowledge the NIH and NIDDK funding and other sources of funding deemed appropriate by the Executive Committee, if any.

For secondary manuscripts without group authorship, the investigators involved in writing the paper will be listed by name followed by "for the Diabetic Retinopathy Clinical Research Network."

For abstracts, the authorship will include the presenter 'for the Diabetic Retinopathy Clinical Research Network'. On a case by case basis, the lead statistician or another individual with substantial input also may be listed as an author.

For the major results manuscript, the DSMC must approve the manuscript prior to submission. The DSMC will be sent secondary manuscripts for comment, but approval will not be required unless requested by the Operations Group.

For each protocol, a dataset will be made available to the public after the main manuscripts are published.

Although it is discouraged, investigators will be permitted to publish their results two years following termination of a study protocol. If an investigator desires to publish his or her results before the end of two years, a request can be submitted to the Executive Committee.

3. Publicity

The Executive Committee must give approval prior to any press release or other publicity about study results that are not yet in the public domain and approval for public use of the Diabetic Retinopathy Clinical Research Network name (See Policy Appendix I: Publicity and Press Releases).

4. Patient Confidentiality

Individual patient medical information obtained as a result of this project is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare in accordance with an institution's policies.

Data generated as a result of this study are to be available for inspection upon request by the Coordinating Center, the NIH, and auditors of regulatory agencies.

5. Policy for Website Use

All study personnel must log onto the DRCR.net website only using their individually created password and must not share their password with others.

A. Electronic Signature

An electronic signature on an electronic case report form indicates that the data have been reviewed and accepted by the signatory. Electronic signatures will consist of the combination of the individually assigned DRCR.net personnel identification number and password. It is unlawful to forge an electronic signature.

Additional information regarding website use can be obtained in the DRCR Website User's Manual.

6. Retention of Study Records

Each center will archive all relevant study data and keep them on file for the period of time specified by US law or by the center's institutional requirements, whichever is greater.

7. Study Participant Retention

The goal for the Network is to have as few losses to follow-up as possible. A study participant has the right to withdraw from a study at any time. If a study participant is considering withdrawal from a study, the investigator must attempt to speak personally to the study participant about the reasons, and make every effort to accommodate the study participant. The Coordinating Center will assist in the tracking of study participants.

8. Patient Costs

Study participants will not be responsible for any medical costs which are part of the protocol that they would not have incurred if they had not participated in the study. Grant funds are intended to pay for study procedures that are purely for research and otherwise would not have been performed as part of routine patient care. All clinical services performed by a physician or staff that would be considered the routine care independent of the study should be billed to the patient or his/her insurance company or both. Funds may be available for certain protocols to cover unreimbursed costs from insurance for study participants with a financial hardship. If a financial hardship does not exist, the DRCR.net cannot reimburse per the Centers for Medicare and Medicaid Services (CMS) policy. Such instances will be reviewed on a case-by-case and procedure-by-procedure basis.

Study participants may be compensated for their participation, subject to IRB approval.

9. Participation of Investigators in 'Competing' Studies

A 'competing' study is defined as one in which subject eligibility criteria overlap with that of a DRCR.net study. Investigators are expected to avoid participation in a competing study if participation is likely to negatively impact a DRCR.net study in which they are participating, such as in subject recruitment or retention or in any other aspect of the study.

Sites are required to inform the Coordinating Center of studies in which they are participating that have eligibility criteria that overlap with a DRCR.net protocol in which they are concurrently participating.

Sites should internally determine a management plan for competing studies. Although sites will not be required to submit a proposed management plan to the Coordinating Center, sites will be provided with the Network's Competing Studies Document (available on the DRCR.net website under Documents) that provides guidance on managing competing studies. In addition, assistance from the Operations Group will be available for sites that would like advice on how to manage their competing studies (See Policy Appendix II: Competing Studies and the DRCR Network).

10. Women and Minorities

It is expected that men and women will be equally represented in all protocols of the project. Efforts will be taken to assure satisfactory minority representation.

11. Funding

A. Clinical Centers

Clinical centers will be funded through subcontracts with the Jaeb Center for Health Research. Funding is expected to be partially on a fixed-cost basis for completion of milestones such as certification for a protocol and primarily on a per-patient basis for the conduct of a protocol. A payment schedule will be established for each protocol.

B. Protocol Chair

The Protocol Chair for a study will be supported through either a subcontract between the Jaeb Center and the Chair's institution or through a consulting agreement and will have responsibility for the scientific aspects of a protocol.

C. Committees

Committee members will receive a monthly consulting payment from the Jaeb Center to partially compensate them for the time they devote to the study in attending meetings, participating in conference calls, pilot testing study procedures, etc.

D. Coordinating Center

The Coordinating Center is funded through a Cooperative Clinical Research Agreement from the Department of Health and Human Services, National Institutes of Health, National Eye Institute to the Jaeb Center for Health Research. Additional funding may be provided to the Jaeb Center for Health Research for Coordinating Center activities by industry, foundations, or unrestricted gifts following approval of the NEI and the Executive Committee.

E. Operations Center

The Operations Center is funded through a Cooperative Clinical Research Agreement from the Department of Health and Human Services, National Institutes of Health, National Eye Institute, currently to the Johns Hopkins University.

F. Vice-Chair(s) and Other Investigator Positions

Vice-Chair(s) and other Investigator Working Positions are funded through the Coordinating Center or Operations Center or through subcontracts of either or both Centers.

12. Supplementary Studies

A supplementary, or ancillary study, is one in which procedures not part of the primary protocol are performed on a subject participating in a current DRCR.net protocol. Any supplementary studies not part of the protocol that are performed on a DRCR.net subject require pre-approval. The purpose of the approval is to assure that the supplementary study will not interfere with the primary study.

There are two main types of supplementary studies.

1) Additional testing for research purposes at a single site where both study resources and the Coordinating Center are not involved
2) A formal protocol to be carried out at one or multiple sites

A. General Principles

1) Any supplementary study must not interfere with the primary protocol
2) Participation must be optional for study subjects
3) Approval by the Executive Committee and Data and Safety Monitoring Committee is required prior to initiation
4) Approval by the Executive Committee is required when network resources are involved, including all supplemental studies that will involve the Coordinating Center.
5) Approval by the IRB is required prior to initiation.

B. Reason for Requirement of Approval

Study Not Requiring Network Resources

For supplementary studies at a single site that do not involve Network resources, the review process will evaluate whether the supplementary study will:

1). Interfere with subject enrollment
2). Interfere with the conduct of the existing protocol
3). Adversely affect subject cooperation
4). Complicate the interpretation of the protocol results

For such studies, the review process will not necessarily focus primarily on scientific merit.

Study Requiring Network Resources

It is anticipated that all multi-site studies will require Network resources for coordination. In addition to the above review criteria, the review process will evaluate the following:

1). Will there be a diversion of Network resources locally or at the Coordinating Center
2). Scientific merit

C. Procedures for Obtaining Supplementary Study Approval

The request for approval of a supplementary study should be in narrative form. It should contain a brief description of the objectives, methods, and significance of the study. Full details should be given concerning any procedures to be carried out on study participants, such as visual function or laboratory procedures. Mention should be made of any substances to be injected or otherwise administered to the study participants. Any observations to be made or procedures to be carried out on a study participant outside of the protocol should be described. Mention should be made of the extent to which the supplementary study will require extra clinic visits by the study participant or that will prolong the study participant's usual clinic visits. The application should indicate whether additional funding is needed and, if yes, list the source of the funding.

The investigator should send the supplementary study request to the Coordinating Center. The Operations Group will review all ancillary study ideas within two months. Ideas deemed feasible and of public health importance to be expedited will be reviewed by the Executive Committee within an additional six to eight weeks. Other ancillary ideas deemed feasible and potentially of public health importance but not judged to be expedited may follow the timeline of new protocol ideas, which are reviewed every six months by the Operations Group. Upon review, a summary of any questions and/or objections raised by members of the Operations Group and Executive Committee will be sent to the applicant so that he/she may amplify, clarify, and/or withdraw the request. If approved by the Executive Committee, the supplementary study also must be reviewed and approved by the Data and Safety Monitoring Committee.

D. Publication of Supplementary Study Results

All manuscripts or presentations for scientific meetings based on supplementary study data must be reviewed and approved by the DRCR.net Executive Committee before publication or presentation. Such review will pertain to expected impact on Network objectives and not to scientific merit alone. Supplemental studies conducted at all DRCR.net sites or conducted at a subset of sites participating in the primary protocol will list on the author line ‘for the DRCR.net’. The publication policy is further detailed in Section 3.

13. Patient Protection and Data Quality

A. Institutional Review Board (IRB)

Each site must obtain approval from an IRB for each protocol in which it participates before it can begin to enroll patients. The site must abide by reporting requirements of the IRB. All changes in the research activities and all unanticipated problems involving risks to patients must be immediately reported. Significant protocol changes require IRB approval before implementation, except when required to eliminate apparent immediate hazards to patients.

IRB coverage must remain current. The Coordinating Center will send a reminder to each site about two months prior to the expiration of IRB coverage for a protocol (a protocol update for the IRB will be included). If IRB coverage lapses, the site cannot enroll any new patients and cannot submit data forms to the Coordinating Center for any established study patients until IRB coverage is back in effect.

For some protocols, individuals who are not at institutions with IRBs may be permitted to use the Jaeb Center IRB.

B. Informed Consent

An informed consent form must be signed by a potential study participant before any procedures are performed that are specific to a study (i.e., not part of a patient’s routine care). If IRB-approved, some protocols may allow verbal consent only. The Informed Consent Form will contain information about the objectives of the study, the procedures followed during the study, and the risks and restrictions of the study, with special reference to possible side effects of the treatments. The form will be in compliance with the guidelines of the Office for Human Research Protections (OHRP) and the IRB. The standard format recommended for most protocols will have two signature lines, one for consent for screening procedures (other than those that are part of routine care) and a second to be signed just prior to randomization, after the potential study participant has had time for careful consideration.

Consent must be obtained according to local IRB procedures. In addition to any local IRB procedures, consent only may be obtained by a DRCR.net investigator or coordinator who is certified through the Coordinating Center for the protocol for which consent is being obtained. If a site wishes to have a non-protocol certified person be certified as a consenter for a protocol and local IRB procedures allow for this possibility, the site should request written approval for this through the Coordinating Center.

For these requests, protocol specific requirements will be established to certify an individual as a consenter for a protocol.

C. Site Visits and Data Audits

The site visit policy may vary from protocol to protocol and will be determined by the Operations Group. The site visits will be coordinated by the Coordinating Center but may include other individuals from both within and outside the study group.

Site visits may be performed on a routine schedule for sites participating in major IND protocols. In general, a site visit will be performed (1) whenever there are concerns about data quality or (2) when an investigator (or site, if there are multiple investigators at the same site) enrolls or is projected to enroll at least 10% of the patients in a protocol, (3) when required by a regulatory agency or (4) when a site is participating in a major IND protocol. All investigators are subject to site visits and must agree to cooperate with site visits in order to participate in DRCR.net protocols.

D. Scientific Fraud

Scientific fraud refers to the situation in which data are actually fabricated. Examples include (1) altering information collected from a patient that would have excluded the patient so that the patient appears to be eligible for the study, (2) randomization of patients prior to obtaining informed consent and changing the date on the informed consent form to conform with the randomization date, (3) changing examination dates so that they appear to be in the time windows specified in the protocol, and (4) altering outcome measurements.

Perfect compliance with the protocol is not expected. Study participant adherence to protocol will never be 100%. Some problems with medication compliance (where applicable) and missed visits are expected in any trial. Some misclassification of outcome is also possible. In fact, in determining a sample size estimate for a study, an adjustment is made to account for the expected losses to follow up, number of misdiagnosed study participants, and number of study participants who do not comply with their treatment assignment.

Clinic staff do make mistakes. Unintentional errors that occur in data collection are not scientific fraud. They may be signs of poor clinic performance and such errors are tabulated by the Coordinating Center, but they do not imply fraud. This is monitored by the Coordinating Center and becomes a concern when a clinic is making more mistakes than expected, particularly major ones (e.g. entering ineligible patients).

An investigator has the responsibility of assuring that the protocol is carried out properly at his/her site and assumes responsibility for staff involved in the care of and data collection for study participants. An investigator who suspects data irregularities should report this to the Coordinating Center immediately.

E. Human Subjects Training

Human subjects training is required every two years by active investigators and coordinators. This refresher test can be completed on the DRCR.net website and is designed to provide investigators and coordinators with a refresher course in the ethics of research and the protection of human subjects. The program consists of an educational tutorial in a question and answer format as well as an interactive test. Individuals at institutions which have similar tests may use that test as a substitute for the DRCR.net test.

F. Provision of Care if a Study-Related Injury Occurs

In general, the DRCR Network does not have a program to pay for study participants who have an adverse event or injury as a result of being in a DRCR Network study. However, DRCR Network investigators, to the best of their abilities, should arrange for necessary medical care for study participants with study-related injuries and provide any medical records from the study they judge are relevant or needed to treat the injury.

14. Confidentiality

Study data, protocols, other documents, and proceedings of meetings and conference calls are considered confidential information until such time that they are reported publicly or placed in the public domain. This includes information that has been received from an outside entity by the Network and labeled as confidential.

Network investigators and staff agree to take all reasonable care to maintain confidential information as secret and confidential, such efforts to be no less than the degree of care employed by the Network investigator or staff to preserve and safeguard his or her own confidential information. The confidential information shall not be disclosed or revealed to anyone except employees of the Network investigator or staff who have a need to know the confidential information for Network activities and who agree to be bound by the Network's policies of confidentiality.

Except as required by law, obligations under Paragraphs 2 and 3 above shall not extend to any part of the confidential information wherein:

- the disclosed information was previously known to the party to whom the disclosure is made as evidenced by written documents; or
- the substance of the disclosure was or becomes general public knowledge; or
- the substance of the disclosure is made known by a third party who by such disclosure is not in breach of any duty or obligation toward the party whose confidential information is being disclosed ; or
- the party providing the confidential information agrees to its disclosure.

Network investigator or staff obligations under Paragraphs 2 and 3 above shall extend for a period of five (5) years from the effective date of receipt of confidential information unless otherwise specified for a specific protocol or committee assignment.

The DRCR.net requires that all new investigators and coordinators sign a Confidentiality Statement upon joining the Network. Investigators and coordinators will be restricted from receiving routine correspondence from the Coordinating Center and attending Network meetings until the Confidentiality Statement has been signed.

15. Financial Disclosure and Conflict of Interest

All DRCR.net investigators, coordinators, committee members, and other key staff personnel will be required to disclose all financial interests and working relationships with any entity whose financial interests potentially could be affected by the conduct or outcome of DRCR.net research. This disclosure will be required on a semiannual basis (January 1st and July 1st) by completion of an electronic financial disclosure form on the DRCR.net website and must be updated within 30 days when there is a new financial disclosure due to a new Network protocol, change in a Network protocol, or a change in the Network investigator or staff's finances. Although the Network requires semiannual disclosure, each disclosure will cover the previous 12 months.

Any person serving as Network Chair or other members of the Executive Committee (or other committees as applicable) who have financial disclosures relevant to a company involved in discussions to collaborate with the Network will forego voting privileges regarding decisions on the collaboration. This policy will prevent putting any DRCR.net investigator in an inappropriate position and will ensure that financial biases are eliminated when voting takes place.

Further details of the Network policy appear in a separate document (Policy Appendix III: Financial Disclosure Policies for the DRCR Network).

16. Guidelines for Remaining as an Active Clinical Site in the Network

It is recognized that some effort is needed to maintain a Clinical Site in the Network, including, for example, site visits, contracts, and IRB issues.

Definitions:

- **Active Clinical Site:** able to enroll study participants in the Network.
- **Inactive Clinical Site:** unable to enroll study participants in the Network but able to follow subjects in the Network.
- **Dropped Clinical Site:** unable to enroll or follow subjects in the Network; not considered part of the Network from the time that the Clinical Site is dropped.

In general, the following minimum activity is expected to maintain a clinical site as active in the Network:

1. Enrollment of at least 1 subject in a Network protocol each calendar year.
    - Sites that do not enroll at least one subject in a Network protocol during a calendar year <u>and</u> have no active study participants in follow up may be ***dropped*** from the Network.
2. Maintenance of certification of a clinic coordinator and visual acuity examiner for the site and any certified technician (e.g., photographer, OCT examiner) needed for participation in protocols in which the site is participating.
    - Sites that do not have sufficient certified personnel will be placed on ***inactive*** status for new enrollments until the deficiency is corrected
3. Participation by the Principal Investigator in at least two Investigator Monthly Teleconferences every 3 months or attendance at an Investigator Meeting in lieu of a Monthly Teleconference.

Individual protocols may have additional criteria for a site to remain active for the protocol.

17. Guidelines for Remaining as an Active Investigator in the Network

It is recognized that some effort is needed to maintain investigator participation in the Network. For example, the Directory needs to be kept up to date; financial disclosure forms must be maintained. Investigators may have had the best of intentions to participate in the Network but then demonstrate little or no activity in any given year.

Definitions:

- **Participating Investigator:** enrolling study participants or follow study participants in the Network or participating in Network committees
- **Dropped Investigator:** unable to enroll or follow study participants in the Network or participate in Network activities, including committees, conference calls and meetings; the Investigator is not considered part of the Network from the time that the Investigator is dropped

In general, the following minimum activity is expected to maintain Investigator participation in the Network:

1. Enrollment of at least 1 study participant in a Network protocol each calendar year or follow-up of at least 1 subject in a Network protocol each calendar year or participation on a Network Committee each calendar year
    - Investigators with no activity during a calendar year may be dropped from the Network.
2. Adherence to Network policy including timely signoff on manuscripts and submission of financial disclosure forms.
3. Participation in at least one Investigator Monthly Teleconference every 3 months or attendance at an Investigator Meeting during a 3-month interval.

Individual protocols may have additional criteria for an investigator to remain active for the protocol.

18. **Industry Collaborations**

The DRCR.net collaborates with Industry in a manner that appreciates the needs of Industry with regard to drug development while maintaining clinical trial design, investigational ethics, and rigorous implementation consistent with academic standards. The DRCR.net has policies related to Industry collaborations, including protocol development, study data, publications, presentations, and publicity, data integrity, clinical sites, site monitoring, adverse event reporting, efficacy and safety reviews, study drug, laboratory measurements, FDA registration and submission, study committees and oversight, legal agreements, and cost sharing. (See Policy Appendix IV: DRCR.net Industry Collaboration Policies for detailed information.)

Appendices

Appendix I: Publicity and Press Releases for the DRCR Network

Appendix II: Competing Studies and the DRCR Network

Appendix III: Financial Disclosure Policies for the DRCR Network

Appendix IV: DRCR.net Industry Collaboration Policies

Appendix V: DRCR.net Organizational Structure