DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK

POLICIES (Version 3.2)

1. Editorial Policy

Each protocol conducted by DRCRnet 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 DRCRnet 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 related to any aspect of the project including but not limited to study protocols, study results, and study conduct must receive the approval of the Steering Committee. The topic for a manuscript may be initiated by the Executive Committee, Steering Committee, or by any participant who may send a suggestion for a paper to the Steering Committee for its review.

Since every investigator cannot have an active role in writing a paper, the Steering Committee will establish a Writing Committee 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 major results paper. A decision on the authorship listing will be made prior to the writing of each manuscript by the Steering Committee. The list may be modified by the Steering Committee prior to manuscript submission to account for unanticipated contribution effort of any individual.

The Steering Committee must approve all manuscripts or abstracts about each study or any ancillary study prior to submission for publication. Abstracts not requiring DSMB approval must be submitted to the Coordinating Center at least two weeks prior to the submission deadline. Abstracts requiring DSMB approval must be submitted to the Coordinating Center at least one month 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 one month prior to the submission date.

For major manuscripts, the authorship listing will include the writing committee and the DRCR.net Study Group. All investigators who participated in the protocol (1) will be given an opportunity to review and comment on the manuscript, (2) will be listed in the manuscript and (3) can include the manuscript on their CVs as a co-author. Each manuscript will acknowledge the NIH funding and other sources of funding, if any.

For abstracts, the authorship will include the presenter and the DRCRnet.

For secondary manuscripts, the investigators involved in writing the paper will be listed by name followed by "for the DRCR.net Study Group."

For the major results manuscript, the DSMB must approve the manuscript prior to submission. The DSMB will be sent secondary manuscripts for comment, but approval will not be required.

For each manuscript, a dataset will be made available after the manuscript is published (unless precluded by contractual arrangements with a protocol sponsor).

Although it is discouraged, investigators will be permitted to publish their results two years following termination of a study protocol.

2. Publicity

The Steering Committee must give approval prior to any press release or other publicity about study results that are not yet in the public domain.

3. 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.

4. Policy for Website Use

All study personnel must log onto the DRCRnet website only using their own 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 combined combination of the individually assigned DRCRnet personnel identification number and password.

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

5. 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.

6. Patient Costs

Study subjects will not be responsible for any costs that they would not have incurred if they had not participated in the study. Grant funds are intended to pay for patient procedures that are purely for research and otherwise would not have been performed. All clinical services performed by a physician or staff that would be considered the routine standard of care independent of the study should be billed to the patient or his/her insurance company.

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

7. 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. Clinical sites 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.

Clinical sites that intend to participate in a competing study will submit a brief statement to the Executive Committee that summarizes the competing study and indicates any potential areas of overlap or conflict with a DRCR.net study in which the clinical site is currently participating or intends to participate.

8. Women and Minorities

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

9. 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.

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.

10. Supplementary Studies

Any testing not part of the protocol or usual medical care that is performed on a DRCR.net patient requires 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 no study resources involved and no involvement of the Coordinating Center.
2) A formal protocol to be carried out at multiple sites

A. General Principles

1) Any additional testing/ancillary study must not interfere with the primary protocol
2) Participation must be optional for study patients
3) Approval by the protocol's Steering 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 patient enrollment

2). Interfere with the conduct of the existing protocol

3). Adversely affect patient cooperation

4). Complicate the interpretation of the protocol results

5). Jeopardize the public image of the network

For such studies, the review process will not focus 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 the patients, such as visual function or laboratory procedures, etc. Mention should be made of any substances to be injected or otherwise administered to the patients. Any observations to be made or procedures to be carried out on a patient 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 patient or will prolong the patient's usual clinic visits. The application should indicate whether additional funding is needed and, if yes, the source of the funding.

The investigator should send the supplementary study request to the Coordinating Center. Within one month, a summary of any questions and/or objections raised by members of the Steering Committee 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 Steering Committee and Executive Committee, the supplementary study must also 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 participating in the primary protocol will list on the author line 'and the DRCR.net'. Studies conducted at a subset of sites will list 'for the DRCR.net'. The publication policy is further detailed in Section 1.

11. 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 the patient before any procedures are performed that are specific to a study (i.e., not part of patient's routine care). 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 patient has had time for careful consideration.

C. Site Visits and Data Audits

The site visit policy may vary from protocol to protocol and will be determined by the Executive Committee. 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 will not be performed on a routine schedule in view of the large number of investigators and for most protocols the small number of patients per investigator. 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 or (3) when required by a regulatory agency. Other sites will be selected at random for site visits. All investigators are subject to site visits and to participate in DRCR.net protocols must agree to cooperate with site visits.

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. Patient adherence 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 patients, and number of patients 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 patients. An investigator who suspects data irregularities should report this to the Coordinating Center immediately.