

1 **DIABETIC RETINOPATHY CLINICAL RESEARCH NETWORK**

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3 **POLICIES (Version 5.0)**

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5 **1. Editorial Policy**

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

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15 All manuscripts to be written and national/international presentations to be made related to any aspect
16 of the project including but not limited to study protocols, study results, and study conduct must
17 receive the approval of the Steering Committee (primary outcome manuscripts) or Executive
18 Committee (secondary outcome manuscripts or methodology manuscripts). The topic for a manuscript
19 or presentation may be initiated by the Executive Committee, Steering Committee, or by any
20 participant who may send a suggestion for a paper (using DRCR.net Manuscript Idea Form) to the
21 Manuscript Working Group who will provide a recommendation to the Steering Committee for its
22 review.

23
24 Since every investigator cannot have an active role in writing a paper, a Writing Committee will be
25 established for each paper. Investigators may volunteer for these writing assignments. Generally, the
26 Protocol Chair will be the lead writer on the Writing Committee of the primary outcome paper. A
27 decision on the authorship listing will be made prior to the writing of each manuscript by the
28 Steering/Executive Committee. The list may be modified by the Steering/Executive Committee prior
29 to manuscript submission to account for unanticipated contribution effort of any individual.

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31 The Steering Committee/Executive Committee must approve all manuscripts or abstracts about each
32 study or any ancillary study prior to submission for publication. Abstracts not requiring DSMC
33 approval must be submitted to the Coordinating Center at least two weeks prior to the submission
34 deadline. Abstracts requiring DSMC approval must be submitted to the Coordinating Center at least
35 one month prior to the submission deadline. If data are needed for the abstract that have not been
36 previously compiled and verified by the Coordinating Center, the Coordinating Center must be
37 contacted at least one month prior to the submission date.

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39 For major manuscripts, the DRCR.net Study Group will be listed as the author on the title page, if this
40 meets with journal approval. The writing committee for the manuscript will be listed. All investigators
41 and coordinators who participated in the protocol (1) will be given an opportunity to review and
42 comment on the manuscript, (2) will be listed in the manuscript (if permitted by the journal) and (3)
43 can include the manuscript on their CVs as a co-author. Each manuscript will acknowledge the NIH
44 funding and other sources of funding, if any.

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46 For secondary manuscripts, the investigators involved in writing the paper will be listed by name
47 followed by “and the DRCR.net Study Group.”

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

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

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55 For abstracts containing data from a Network-wide protocol, the authorship will include the presenter
56 and the DRCR.net. For abstracts related to a limited number of sites, the authorship will include the
57 presenter and 'for the DRCR.net'.

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

62 63 **2. Publicity**

64 The Steering Committee (Executive Committee for secondary manuscripts) must give approval prior to
65 any press release or other publicity about study results that are not yet in the public domain.

66 67 **3. Patient Confidentiality**

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

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

75 76 **4. Policy for Website Use**

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

79 80 **A. Electronic Signature**

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

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

87 88 **5. Retention of Study Records**

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

91 92 **6. Subject Retention**

93 The goal for the Network is to have as few losses to follow-up as possible. A subject has the right to
94 withdraw from a study at any time. If a subject is considering withdrawal from a study, the
95 investigator should speak personally to the subject about the reasons, and every effort should be made
96 to accommodate the subject. The Coordinating Center will assist in the tracking of subjects.

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7. Patient Costs

Study subjects 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.

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

8. 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.

9. 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.

10. 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.

144 **11. Supplementary Studies**

145 A supplementary, or ancillary study, is one in which procedures not part of the primary protocol are
146 performed on a subject participating in a current DRCR.net protocol. Any supplementary studies not
147 part of the protocol that are performed on a DRCR.net subject requires pre-approval. The purpose of
148 the approval is to assure that the supplementary study will not interfere with the primary study.
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150 There are two main types of supplementary studies.

151 1) Additional testing for research purposes at a single site where no study resources involved
152 and no involvement of the Coordinating Center.

153 2) A formal protocol to be carried out at one or multiple sites
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155 **A. General Principles**

156 1) Any supplementary study must not interfere with the primary protocol

157 2) Participation must be optional for study subjects

158 3) Approval by the protocol's Steering Committee and Data and Safety Monitoring Committee
159 is required prior to initiation

160 4) Approval by the Executive Committee is required when network resources are involved,
161 including all supplemental studies that will involve the Coordinating Center.

162 5) Approval by the IRB is required prior to initiation.
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164 **B. Reason for Requirement of Approval**

165 **Study Not Requiring Network Resources**

166 For supplementary studies at a single site that do not involve Network resources, the review process
167 will evaluate whether the supplementary study will:
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169 1). Interfere with subject enrollment

170 2). Interfere with the conduct of the existing protocol

171 3). Adversely affect subject cooperation

172 4). Complicate the interpretation of the protocol results
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174 For such studies, the review process will not focus on scientific merit.
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176 **Study Requiring Network Resources**

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

179 1). Will there be a diversion of network resources locally or at the Coordinating Center

180 2). Scientific merit
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182 **C. Procedures for Obtaining Supplementary Study Approval**

183 The request for approval of a supplementary study should be in narrative form. It should contain a
184 brief description of the objectives, methods, and significance of the study. Full details should be given
185 concerning any procedures to be carried out on the patients, such as visual function or laboratory

186 procedures, etc. Mention should be made of any substances to be injected or otherwise administered to
187 the subjects. Any observations to be made or procedures to be carried out on a subject outside of the
188 protocol should be described. Mention should be made of the extent to which the supplementary study
189 will require extra clinic visits by the patient or will prolong the patient's usual clinic visits. The
190 application should indicate whether additional funding is needed and, if yes, the source of the funding.
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192 The investigator should send the supplementary study request to the Coordinating Center. Within one
193 month, a summary of any questions and/or objections raised by members of the Steering Committee
194 and Executive Committee will be sent to the applicant so that he/she may amplify, clarify, and/or
195 withdraw the request. If approved by the Steering Committee and Executive Committee, the
196 supplementary study must also be reviewed and approved by the Data and Safety Monitoring
197 Committee.
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199 **D. Publication of Supplementary Study Results**

200 All manuscripts or presentations for scientific meetings based on supplementary study data must be
201 reviewed and approved by the DRCR.net Executive Committee before publication or presentation.
202 Such review will pertain to expected impact on network objectives and not to scientific merit alone.
203 Supplemental studies conducted at all DRCR.net sites participating in the primary protocol will list on
204 the author line 'and the DRCR.net'. Studies conducted at a subset of sites will list 'for the DRCR.net'.
205 The publication policy is further detailed in Section 1.
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207 **12. Patient Protection and Data Quality**

208 **A. Institutional Review Board (IRB)**

209 Each site must obtain approval from an IRB for each protocol in which it participates before it can
210 begin to enroll patients. The site must abide by reporting requirements of the IRB. All changes in the
211 research activities and all unanticipated problems involving risks to patients must be immediately
212 reported. Significant protocol changes require IRB approval before implementation, except when
213 required to eliminate apparent immediate hazards to patients.
214

215 IRB coverage must remain current. The Coordinating Center will send a reminder to each site about
216 two months prior to the expiration of IRB coverage for a protocol (a protocol update for the IRB will
217 be included). If IRB coverage lapses, the site cannot enroll any new patients and cannot submit data
218 forms to the Coordinating Center for any established study patients until IRB coverage is back in
219 effect.
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221 For some protocols, individuals who are not at institutions with IRBs may be permitted to use the Jaeb
222 Center IRB.
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224 **B. Informed Consent**

225 An informed consent form must be signed by the patient before any procedures are performed that are
226 specific to a study (i.e., not part of patient's routine care). The Informed Consent Form will contain
227 information about the objectives of the study, the procedures followed during the study, and the risks
228 and restrictions of the study, with special reference to possible side effects of the treatments. The form
229 will be in compliance with the guidelines of the Office for Human Research Protections (OHRP) and
230 the IRB. The standard format recommended for most protocols will have two signature lines, one for
231 consent for screening procedures (other than those that are part of routine care) and a second to be
232 signed just prior to randomization, after the patient has had time for careful consideration.
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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 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. Subject 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 subjects, and number of subjects 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 subjects. An investigator who suspects data irregularities should report this to the Coordinating Center immediately.

13. 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

282 INFORMATION for Network activities and who agree to be bound by the Network’s policies of
283 confidentiality.

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285 Except as required by law, obligations under Paragraphs 2 and 3 above shall not extend to any part of
286 the CONFIDENTIAL INFORMATION wherein:

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

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

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299 **14. Financial Disclosure and Conflict of Interest**

300 All investigators and other key personnel will be required to disclose all financial interests and
301 working relationships which may constitute or be perceived to constitute a conflict of interest with this
302 project. This disclosure will be required on an annual basis by completion of a form provided by the
303 Network as well as at the time of initiation of new protocols, and must be updated within 30 days when
304 there is a new potential conflict due to a change in a Network protocol or a change in the Network
305 investigator or staff’s finances. Further details of the Network policy appear in a separate document
306 (“Conflict of Interest Policies”).

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308 **15. Guidelines for Remaining as an Active Clinical Site in the Network**

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

311 Definitions:

- 312 • **Active Clinical Site:** able to enroll subjects in the Network.
- 313 • **Inactive Clinical Site:** unable to enroll subjects in the Network but able to follow subjects in
314 the Network.
- 315 • **Dropped Clinical Site:** unable to enroll or follow subjects in the Network; not considered part
316 of the Network from the time that the Clinical Site is dropped.

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

319 1. Enrollment of at least 1 subject in a Network protocol each calendar year.

- 320 • Sites that do not enroll at least one subject in a Network protocol during a calendar year
321 and have no active subjects in follow up will be **dropped** from the Network.

- 322 • Sites that do not enroll at least one subject in a Network protocol during a calendar year
323 but have active subjects in follow up will be placed on *inactive* status.
- 324 2. Maintenance of certification of a clinic coordinator and visual acuity examiner for the site and
325 any certified technician (e.g., photographer, OCT examiner) needed for participation in
326 protocols in which the site is participating.
- 327 • Sites that do not have sufficient certified personnel will be placed on *inactive* status for
328 new enrollments until the deficiency is corrected
- 329 3. Participation by the Principal Investigator in at least two Investigator Monthly Teleconferences
330 every 3 months or attendance at an Investigator Meeting in lieu of a Monthly Teleconference.

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332 **16. Guidelines for Remaining as an Active Investigator in the Network**

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

337 Definitions:

- 338 • **Participating Investigator:** enrolling subjects or follow subjects in the Network or
339 participating in Network committees
- 340 • **Dropped Investigator:** unable to enroll or follow subjects in the Network or participate in
341 Network activities, including committees, conference calls and meetings; the Investigator is not
342 considered part of the Network from the time that the Investigator is dropped

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

- 346 1. Enrollment of at least 1 subject in a Network protocol each calendar year or follow-up of at
347 least 1 subject in a Network protocol each calendar year or participation on a Network
348 Committee each calendar year
- 349 • Investigators with no activity during a calendar year may be dropped from the Network.
- 350 2. Adherence to Network policy including timely signoff on manuscripts and submission of
351 conflict of interest forms.
- 352 3. Participation in at least one Investigator Monthly Teleconference every 3 months or attendance
353 at an Investigator Meeting during a 3-month interval.