Policy Appendix IV: DRCR.net Industry Collaboration Policies

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DRCR.net is committed to:

- performing rigorous multi-center clinical trials to address timely critical needs in diabetic retinopathy and diabetic macular edema
- collaborating 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 sections below outline the DRCR.net policies with regard to industry collaboration.

A. Protocol Development

1. DRCR.net will develop the protocol according to Network standards (including associated procedures, CRFs, statistical plan, etc.).

2. The industry partner may provide input, especially with regard to regulatory issues when the protocol is being conducted under an IND.

3. DRCR.net will accommodate industry partner needs required for drug registration as long as they are feasible and maintain clinical trial design and implementation consistent with academic standards.

4. DRCR.net will consider expanding protocols with additional industry support to provide adequate size such that industry can analyze data as two definitive trials according to FDA guidance if so requested by the industry partner.

5. All final decisions regarding protocol design, development and implementation will be made by DRCR.net.

6. The protocol will be placed in the public domain at the commencement of the study. The protocol will be posted on the DRCR.net public website and summarized on public websites such as clinicaltrials.gov.

B. Study Data

1. DRCR.net will have ownership of the study data.

2. The final dataset will be placed in the public domain.

3. At the completion of the study, DRCR.net will distribute a final dataset to the industry partner for its needs regarding FDA submission (as a general rule, DRCR.net does not intend to prepare FDA submissions itself) and its internal use. The dataset may not be used for any other purpose unless approved by DRCR.net.

C. Publications, Presentations, and Publicity

1. DRCR.net is free to publish and present the study data without restriction.

2. DRCR.net will provide the industry partner with the opportunity to review and comment on the primary manuscript and any secondary manuscript that provides information related specifically to the treatment under study that is not already in the public domain. This policy also applies to abstracts and presentations that are made prior to the information having already been publicly disseminated. Unless DRCR.net and the industry partner agree on different time intervals, the

industry partner will be given 14 days to comment on manuscripts and up to an additional 30 days if there is a need for the industry partner to submit patent application materials to obtain patent protection.

3. DRCR.net will have the opportunity to review and comment on all press releases of the industry partner related to the study prior to their release. The industry partner will not release information about the study without the review and comment of DRCR.net.

4. The industry partner may not publish or present any study results that have not already been publicly disseminated by DRCR.net

D. Data Integrity

1. The DRCR.net Coordinating Center will oversee data collection, data cleaning, data lock, data maintenance, etc. DRCR.net utilizes electronic data capture such that the electronic capture is the source documentation

2. DRCR.net will provide the industry partner with details of these procedures for the industry partner to verify that these procedures meet regulatory requirements.

3. The industry partner may conduct a yearly site visit of the Coordinating Center to evaluate issues related to maintaining the database and other Coordinating Center procedures as they pertain to meeting regulatory requirements.

E. Clinical Sites

1. The DRCR.net will select the participating sites and establish the procedures for their certification. Certification includes the review and approval of regulatory documents such that the clinical site is approved to receive study drug and subsequently enroll patients.

2. The industry partner may review these procedures to verify that they are in accord with regulatory requirements.

3. The DRCR.net Coordinating Center will be responsible for the certification of the sites.

F. Site Monitoring

1. DRCR.net will determine those monitoring needs it deems critical for the study and provide the support needed.

2. The industry partner may review the DRCR.net site monitoring plan to verify that it meets regulatory requirements.

3. The industry partner will not be permitted to contact the clinical sites, request data or conduct monitoring visits without approval from DRCR.net. Permission may be granted in the event of a pending FDA audit.

4. If the industry partner determines that additional monitoring is needed for regulatory purposes, DRCR.net will consider this request but will have the right to reject the request. Support for any additional monitoring will be provided by the industry partner.

5. The monitoring will be overseen by the DRCR.net Coordinating Center, which will have the option of conducting this monitoring itself.

G. Adverse Event Reporting

1. DRCR.net will establish a system for adverse event reporting, review, and coding.

2. The industry partner may review this plan to verify that it is in accord with regulatory requirements and will meet the industry partner's needs for its FDA submission.

H. Efficacy and Safety Reviews, Stopping Decisions

1. DRCR.net will be responsible for developing the statistical analysis plan.

2. The industry partner may review this plan to verify that it is in accord with regulatory requirements and will meet the industry partner's needs for its FDA submission.

3. An independent Data and Safety Monitoring Committee (DSMC) will review all data (masked or unmasked) as appropriate and make suggestions to the DRCR.net regarding protocol modifications and stopping a study for efficacy or safety. The industry partner will not be provided with the study data (other than the aforementioned masked adverse event data) until either the conclusion of the study or the DSMC's decision that such data can be provided.

4. DRCR.net will provide the industry partner with monitoring reports related to study progress (such as a recruitment report by month).

I. Study Drug

1. The industry partner will be responsible for providing the study drug, placebos (when applicable), packaging of the drug, all necessary manufacturing information for the IND and any related materials. The industry partner will agree to provide the drug and related materials for the duration of the study.

2. Study drug will be manufactured in accordance with GLP and GMP standards.

3. The DRCR.net will develop procedures for supplying the drug to the clinical sites, maintaining accountability of the study drug at the site, and disposal of the drug. The industry partner will pay for the costs of supplying drug to the clinical sites and returning drug for disposal. The industry partner, if requested, will supply the drug and related materials directly to the clinical sites.

J. Laboratory Measurements

1. DRCR.net will determine those laboratory measures it deems necessary for the study.

2. The industry partner may identify those additional laboratory measures required for regulatory or other purposes. DRCR.net will attempt to accommodate these needs as long as they do not adversely effect the conduct, data validity or safety of the study.

3. DRCR.net will have the final decision on the use of a central laboratory.

K. FDA Registration and Submission

1. DRCR.net will have the option of applying for and maintaining the IND. The industry partner will assume this function if requested by DRCR.net.

2. The industry partner will perform registration and submission specific analysis and preparation as needed.

3. DRCRnet and the industry partner will provide one another with a copy of all documents submitted under the IND.

4. Should there be a need to conduct a second trial specifically for the purpose of the FDA submission, the industry partner will have the option of conducting the second trial independently from the DRCR.net or may contract with the DRCR.net to conduct the second trial as long as DRCR.net agrees that such a trial is an appropriate use of DRCR.net resources at that time.

L. DRCR.net Policies

1. The industry partner will be provided with a copy of the DRCR.net policies and the Terms and Conditions of the NEI Cooperative Agreement.

M. Study Committees and Oversight

1. The industry partner will appoint an individual to serve as the liaison with the DRCR.net.

2. The liaison will receive recruitment reports on the progress of the study.

N. Legal Agreements

1. A legal agreement will be established between the industry partner and the Coordinating Center.

2. A legal agreement will be established between the Coordinating Center and each participating site for the site's participation in the study.

3. The legal agreement will contain an indemnification section that specifies, the situations in which the industry partner will provide indemnification, a confidentiality section agreeable to both parties, and an intellectual property section agreeable to both parties.

O. Cost Sharing

1. DRCR.net will usually provide funding along with collaborators, for studies that are:
   - associated with one definitive efficacy trial per specific intervention that meets DRCR.net standards
   - associated with earlier stage trials (e.g.. dose-ranging) or other trial designs as deemed appropriate by DRCR.net

2. DRCR.net will usually not support clinical trial costs that are:
   - not necessary for optimal academic clinical trial design and implementation (eg. additional monitoring, special laboratory analyses, etc.)
   - associated with additional patient numbers required by the industry partner (eg. to have enough power to analyze data as two definitive trials according to FDA guidance)
   - second trials required for IND, registration submission, etc. that do not add significant additional academic scientific information to that provided by prior trials.

3. DRCR.net funding, in general, will provide for the Coordinating Center, Operations Center, Network Chair, Network Vice-Chairs, Protocol Chairs, Executive Committee, Data and Safety Monitoring Committee, and certain infrastructure costs at the clinical centers.

4. In general, the industry partner will be expected to provide funding for:
   - All costs for the clinical sites to conduct the protocol, through a subcontract with the Jaeb Center, including IRB costs
   - All costs involved with the manufacture, labeling, distribution, and disposal of study drug and any other related costs associated with the treatment
   - All costs associated with image grading or other protocol-approved analyses (e.g., pathology, genetic, pharmacokinetic)
   - All laboratory costs
   - Site monitoring costs for site visits and other activities over and above what DRCR.net will be performing
   - All costs involved related to FDA and other regulatory agencies
   - All costs involved for PK study or other preclinical or ancillary studies mutually agreed upon by DRCR.net and the industry partner