PEDIATRIC EYE DISEASE INVESTIGATOR GROUP (PEDIG) POLICIES
Revised April 13, 2018

I. Funding

Major studies are funded through cooperative agreements between the National Eye Institute (NEI) and the Jaeb Center for Health Research.

Other sources of funding may be sought to cover PEDIG expenses or additional studies upon approval of the NEI and the Executive Committee.

A. Funding for Clinical Sites

Each investigator must have a signed agreement between his/her institution or legal entity and the Jaeb Center. The agreement will indicate the payment schedule for participation in each protocol and the obligations of the investigator and institution. A payment schedule will be established for each protocol and payments vary depending upon the level of complexity of the study in terms of time necessary.

Sites are compensated on a per-patient basis for their participation in a protocol. Generally, funding will be provided for each enrollment and each follow-up visit, or phone call/chart review data collection.

B. Committees

Committee members not already compensated for percent effort through a subcontract with the Jaeb Center may receive a consulting payment to partially compensate them for the time they devote to the committee in attending meetings, participating in conference calls, review of materials or other activities associated with the committee.

C. Patient Costs

Grant funds are intended to pay for clinical and other procedures that are purely for research and otherwise would not have been performed on the patient. Most PEDIG protocols will be established to conform to standard medical care as closely as possible. The per-patient funding provided to the site is expected to cover the additional time necessary on the part of the investigator and his/her office staff. This per-patient funding is also expected to cover the costs of maintaining an Internet connection and usage time and study-directed time on the part of the investigator in areas such as promoting recruitment, screening patients who would otherwise not be examined, educating the parents or guardians of eligible patients about the study and obtaining informed consent, responding to calls from the parents or guardians during the study, and addressing edits and queries from the Coordinating Center.

When a care provider performs services that would be considered routine standard of care independent of the study, it is appropriate to bill the patient's insurance company for these services.

Research funds will be used to pay for supplies, medications, spectacles, etc. that would not be required as part of the patient's routine care.

In some studies, patients may be compensated to cover visit-related costs. Generally, a distinction will be made between usual-care visits for which compensation is not typically provided and protocol-required visits for which compensation for the study visit per se will be provided.

D. Participation of Investigators in 'Competing' Studies

Competing studies are defined as those with overlapping eligibility criteria. To ensure that human subjects issues are appropriately addressed, if a PEDIG site is involved in competing studies, the site should submit a brief statement to the Operations Committee that summarizes the studies and describes how the site will manage both studies. For example, which patients will be offered enrollment into one study versus the other? Participation in the PEDIG study will be contingent on OC approval.

E. Financial Disclosure Policies

A significant financial interest (SFI) is defined as such: if it could directly and significantly affect the design, conduct, or reporting of research. PEDIG has developed a policy to avoid financial conflict of interest (FCOI) within the group. The PEDIG policy on avoiding FCOI within the group requires disclosure of any SFI paid directly to the investigator or to the investigator's institution/legal entity on the investigator's behalf in which the investigator has equity. The Operations Committee reserves the right to assess all disclosures as to whether a potential FCOI exists. The following includes PEDIG's policy on avoiding FCOI within the group:

- Investigators with a non-research SFI that exceeds $5,000 with an entity related to PEDIG research are presumptively prohibited from enrolling participants into an applicable PEDIG study that involves more than minimal risk.
- Investigators with a non-research SFI with an entity related to PEDIG research are presumptively prohibited from enrolling more than 10% of the study participants in any applicable PEDIG study.
- The Director of the PEDIG Coordinating Center and the Network Chair are presumptively prohibited from having a non-research SFI with an entity related to PEDIG research.
- Members of the Operations Committee are presumptively prohibited from having a non-research SFI with an entity related to PEDIG research.
- No more than 50% of the members of any protocol development committee, or any writing committee should have a non-research SFI with an entity related to the work being conducted for the specific PEDIG research.
- Members of the Data and Safety Monitoring Committee are presumptively prohibited from having a non-research SFI with an entity related to PEDIG research for which the DSMC is monitoring.

The determination of whether a FCOI exists in certain instances can be a matter of judgment involving all the facts of the situation. The Network Chair and Director of the Coordinating Center will oversee review of potential FCOI. When necessary the Executive Committee will provide final decisions on behalf of the network.

II. Selection of Protocols

A. Process

A process has been developed for evaluation and prioritization of protocols within the PEDIG network.

- Any PEDIG investigator may propose a protocol.
- The protocol proposal form is available on the PEDIG website.
- A formal solicitation to the study group for new study ideas is made in November of each

year, in preparation for review of new study ideas at the Winter PEDIG Study Group meeting.

- Open discussion of ideas occurs at PEDIG investigator meetings (i.e., American Academy of Ophthalmology, American Academy of Optometry, AAPOS, and both the Summer and Winter PEDIG Investigator meetings)
- Each winter, the PEDIG Executive Committee selects up to 15 of these potential studies for further development, based on public health impact and investigator group interest.
- Members of the Operations Committee, in consultation with the Coordinating Center and primary proponents of each proposal, will oversee the creation of a brief protocol proposal (5-7 pages each) that addresses the following:
    - Background, significance, and public health importance
    - Protocol outline (including flow diagram, if applicable)
    - Outcome measures
    - Sample size and statistical considerations
    - Recruitment potential
- The PEDIG Executive Committee will meet for one day each spring to evaluate these protocol proposals and to determine which studies should have full protocols developed and the timeline for their development.
- Feedback will be given to the proponents of each protocol. Those protocols that were not selected may be brought forward for consideration in future cycles. A planning committee will be formed to develop a full protocol for each protocol selected.
- Each fully developed protocol will be circulated to all PEDIG investigators for input prior to final review and approval by the PEDIG Executive Committee and the Data Safety and Monitoring Committee (DSMC), if applicable. An additional step of external review may be necessary prior to review by the DSMC, at the discretion of the NEI.
- The cycle of study idea solicitation, discussion, Executive Committee review, protocol selection and development is repeated yearly.
- If a previously prioritized protocol is not launched during the preceding year, the protocol idea will be brought back for re-consideration at the next EC prioritization meeting, because other new protocol ideas may be deemed to be more important for PEDIG to pursue.

Occasionally, a protocol proposal may have extremely high public health importance and may be prioritized by the Executive Committee for rapid development and implementation outside the yearly cycle described above.

III. 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 patients can be enrolled. The site must abide by the reporting requirements of the IRB. All changes in research activities and all unanticipated problems involving risks to patients must be reported immediately. Protocol changes require IRB approval before implementation, except when required to eliminate apparent immediate hazards to patients. Modifications to study procedures, which do not constitute a meaningful change in the protocol and do not impact in any way on patient safety, do not require prior IRB approval.

IRB coverage must remain current. The Coordinating Center will send a reminder to each site

approximately 2 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, cannot perform study specific procedures on enrolled subjects, and cannot submit data forms to the Coordinating Center for any established study patients until IRB coverage is back in effect.

Individuals who are not at institutions with their own IRB are permitted to use the Jaeb Center IRB.

B. Informed Consent

An informed consent form must be signed by the parent/guardian 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.

C. Policy for Website Use

All study personnel must log onto the PEDIG website only using their individually created password and must not share their password with others. Under no circumstances may an investigator delegate signing of study forms to an assistant who logs in using the investigator's password.

1. 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 PEDIG personnel identification number and password. It is unlawful to forge an electronic signature.

D. Data Quality

Each site is monitored for adherence to the protocol and good clinical practices. Sites or study group members with excessive protocol deviations and/or quality issues may be placed on probation for a period of time and/or dismissed from PEDIG at the discretion of the Executive Committee.

Site visits will be conducted to ensure quality. The site visit policy may vary from study to study and will be determined by the Operations Committee. In general, a site visit will be performed annually, but may occur more often when: (1) there are concerns about data integrity; (2) a site enrolls or is projected to enroll at least 10% of the patients in a study; or (3) a site enrolls a subject into a study covered by an IND. All sites are subject to site visits and, to participate in PEDIG, they must agree to cooperate for site visits.

E. Scientific Fraud

Scientific fraud refers to the situation where 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 as being in the time windows specified in the protocol, and (4) altering outcome measurements.

Although the goal of every study is to have perfect compliance with every aspect of the protocol, this is not always possible. Patient adherence will never be 100%. Problems will occur with medication compliance (where applicable) and missed visits. Misclassification of the outcome is also possible. In determining a sample size estimate for the study, an adjustment is made to account for expected losses to follow up, number of misdiagnosed patients, and number of patients who do not comply with their treatment assignment.

It is expected that clinic personnel will make mistakes. Unintentional errors that occur in data collection are not scientific fraud. Repeated mistakes may be a sign of poor clinic performance and these are tabulated by the Coordinating Center, but they do not imply fraud. Errors become a concern when a clinic is making more mistakes than expected, particularly major ones (e.g., enrolling ineligible patients).

An investigator has the responsibility of assuring that the protocol is carried out properly at their site and assumes responsibility for the staff involved in the care of and data collection for study patients. An investigator who suspects data irregularities should report this to the CC immediately.

Study group members are expected to remain in good standing with their profession. If a study group member fails to adhere to the ethical standards of their profession, the Executive Committee may revoke study group membership.

F. Confidentiality

Individual patient medical information obtained as a result of a study is considered confidential and disclosure to third parties other than those noted below (or on the informed consent) 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. Data generated as a result of studies are to be available for inspection upon request by the Coordinating Center, the NIH, and auditors of other regulatory agencies.

All sites and PEDIG units must conform to HIPAA regulations.

Study data are considered confidential until presented at a national meeting or published as an abstract or manuscript.

G. Retention of Study Records

The principal investigator at each site will archive all relevant study data and keep them on file for the period of time specified by US law or by their IRB, whichever is longer.

IV. Communications

For most protocols, real-time internet access will be required for data entry of case report forms.

V. Study Group Meetings

Study group meetings are planned each year for participating study group members. These meetings may be used to; develop and approve primary study manuscripts, to help refine protocols in development, and to review procedures and issues of ongoing protocols. The PEDIG Operations Committee will define which study group members are invited, but in general study personnel from sites meeting the networks policy on site activity (see section VII. A.) will

be eligible for invitation. The costs of their attendance will be reimbursed, including hotel, airfare and a per diem.

General PEDIG meetings may be held in conjunction with the American Academy of Ophthalmology, American Academy of Optometry, and AAPOS meetings. Each investigator is expected to attend at least one of these meetings yearly. Generally there will be a meeting for all PEDIG investigators at which the status of current and planned protocols will be discussed and topics for possible future studies will be presented. Separate meetings on the same day may be held for investigators participating in specific protocols as needed.

VI. Editorial Policy

A. Manuscripts

The methods and results of each protocol conducted by PEDIG will be reported in one or more manuscripts. Ownership of the data collected as part of all network protocols resides with the investigators. These data are confidential and may not be presented or published by individual investigators. Datasets are maintained at the Jaeb Center and released for reporting in publications and presentations according to the policies below. If an investigator wishes to include PEDIG study subjects in his/her own research publication or presentation, there cannot be overlap with respect to PEDIG study objectives, which are stated in study protocols that are available on the PEDIG web site. If there is possible overlap with respect to PEDIG study objectives, a request should be submitted to the Executive Committee.

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 all 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 (or Executive Committee, if no Steering Committee applies) and the Operations Committee. The topic of the manuscript may be initiated by the Executive Committee, Steering Committee, Operations Committee, or by an investigator.

Because every investigator cannot have an active role in writing every paper, the Operations Committee will establish a Writing Committee and select a Writing Committee Chair for each manuscript.

For major manuscripts, PEDIG will be listed as the author on the title page, if this meets with journal approval; or "Study XXX Investigators for PEDIG", if the journal does not allow PEDIG as the author. The writing committee will be listed with the Writing Committee Chair as first author, followed by other primary authors, including the study statistician. Writing committee members (other than primary authors) will be listed based upon level of contribution to the manuscript, and then by order of number of subject's completing primary outcome exam for the study as applicable. The authorship listing for the writing committee will be suggested by the Operations Committee member assigned to the manuscript, in consultation with the Writing

Committee Chair(s) and the Study Statistician. The list may be modified by the Operations Committee to recognize other contributions.

All investigators who participated in the protocol (1) will be given an opportunity to review and comment on the draft manuscript, (2) will be listed in the manuscript participant appendix, and (3) may include the manuscript on their CVs as a co-author. Each manuscript will acknowledge the NIH funding and any other sources of funding.

For a secondary manuscript, the investigators involved in writing the paper will be listed by name (ordered as described above) followed by "for the Pediatric Eye Disease Investigator Group." The policy on author order will follow that of primary manuscripts (as previously described).

For studies conducted within PEDIG by a subset of sites, the investigators will be listed as authors followed by "for Pediatric Eye Disease Investigator Group" as long as the number of authors does not exceed the journal limit. If the subset of sites is a named group (e.g., COMET), the group will be listed as the author followed by "for Pediatric Eye Disease Investigator Group". The definition of 'subset of sites' will be decided by the PEDIG Executive Committee on a case-by-case basis.

For a manuscript describing the major results of a protocol, the DSMC must approve it prior to submission. The DSMC may be sent secondary manuscripts for comment as determined by the Executive Committee, but approval will not be required.

B. Abstracts

All abstracts must be approved by the Operations Committee prior to submission. Abstracts requiring DSMC approval (major results manuscripts) must be submitted to the Coordinating Center at least 8 weeks prior to the submission deadline. Abstracts not requiring DSMC approval must be submitted to the Coordinating Center at least 4 weeks 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 8 weeks prior to the submission date.

For an abstract associated with a manuscript, the entire writing committee will be listed as authors, if possible. If not possible, the presenter will be listed as the author, followed by lead authors including statistician if applicable, on behalf of the Pediatric Eye Disease Investigator Group. When an abstract is not associated with a manuscript, the authors will be those who worked on the abstract.

C. Presentations

1. PEDIG Authored Presentations

When PEDIG is listed as an author for any presentation at any meeting, investigators or coordinators must forward their presentation for review by the Operations Committee at least 4 weeks before the presentation.

2. Other National and International Presentations

When investigators or coordinators present new PEDIG data (not previously published or

presented) at any national or international meeting, they **must** forward their slides to the Operations Committee for review at least 4 weeks before the presentation.

When investigators or coordinators present publically available PEDIG data (previously published or presented) at any national or international meeting, they **may** (at their own discretion) forward their slides to the Operations Committee for review, and, if they do so, this should be at least 4 weeks before the presentation.

3. Institutional, Local, and Regional Presentations

Investigators or coordinators presenting published PEDIG data at institutional, local, and regional meetings are strongly encouraged to use the slides available on the PEDIG website, but are not required to submit their slides for approval to the Operations Committee, if the presentation is to an institutional, local or regional group.

4. Providing Slides to the Trade Press

PEDIG-authored slides, and slides approved by the Operations Committee, should **not** be provided to the trade press. If the trade press elects to report the results from a PEDIG presentation, and informs the investigator or coordinator of their intentions, the investigator or coordinator may review the draft text for factual errors, but should avoid allowing the journalist to report "in collaboration with….or reviewed by…." Any press release or publicity about a specific study is subject to review and approval prior to release as described in the following section.

D. Publicity

For publicity timed with publication of primary study results, the involved Steering Committee and the Executive Committee must give approval prior to any press release or other publicity about the study. For NEI-funded studies, the DSMC and NEI also must approve release of study findings to the media.

Requests for comment or press releases on behalf of PEDIG on results already published or presented require review of the protocol chair responsible for the study; and the network chair if the protocol chair is not a member of the Operations Committee.

PEDIG investigators may develop mailings to promote study recruitment. These mailings must be approved by the IRB and the PEDIG Operations Committee.

Participation in the PEDIG network may be mentioned in other mailings, web-postings, and publicity materials to the extent that involvement is accurately portrayed. It is important that such mailings not be construed as citing PEDIG involvement for self-promotion and that such mailings do not include remarks that might be considered disparaging by other investigators in the network.

Any letter, flyer or other such promotional material must be reviewed by the Operations Committee prior to distribution. If PEDIG is providing funds for distribution of such mailings, we will inform nearby sites and give them the right to be included in the mailing or offer them the opportunity to distribute something similar. However, if PEDIG is not funding the distribution of such mailings, we would check the mailing for accuracy but cannot require other sites to be listed.

VII. Maintenance of Active Status

A. Site Status

The Executive Committee will evaluate the types of active protocols before the end of each year in order to define for the following year the minimum amount of activity with respect to enrollment and/or follow-up each site is expected to complete to maintain active site status within the network.

Sites that have not met the activity requirement in a 12-month period will be made inactive and their investigators and coordinators cannot attend expenses-paid group meetings. Once a site is made inactive, the site has to reapply for PEDIG site status.

New sites must be certified for their first protocol within 12 months of being accepted as a PEDIG site. Certification efforts at the Coordinating Center will end after 12 months.

VIII. Industry and Other Entity Collaborations

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

Appendices

Appendix I: PEDIG Industry Collaboration Policies

Policy Appendix I: PEDIG Industry Collaboration Policies

Version 1.0, April 13, 2018

The Pediatric Eye Disease Investigator Group (PEDIG) is a collaborative network dedicated to facilitating multicenter clinical research in strabismus, amblyopia, and other eye disorders that affect primarily children. PEDIG is committed to collaborating with companies in a manner that appreciates the needs of industry with regard to drug or device development while maintaining rigorous clinical trial design and implementation, and investigational ethics, consistent with academic standards.

The sections below outline the PEDIG guidelines with regard to collaboration with a company (subsequently referred to as the Company). Depending on the type of collaboration, some of the guidelines below may not apply, while others might need to be developed.

A. Protocol Development

1. In collaboration with the Company, PEDIG will develop the protocol according to PEDIG Network standards (including associated procedures, CRFs, statistical plan, etc.).

2. PEDIG will accommodate Company needs required for drug or device registration as long as they are feasible and clinical trial design and implementation consistent with academic standards is maintained.

3. If requested by the Company, PEDIG will consider expanding protocols with additional Company support to provide adequate size such that the Company can analyze data as two or more definitive trials according to FDA guidance.

4. The PEDIG Executive Committee will need to approve the protocol design and implementation plan.

5. The protocol will be placed in the public domain at the start of the study. The protocol will be posted on the PEDIG public website and summarized on public websites such as clinicaltrials.gov.

B. Study Data

1. PEDIG will have ownership or co-ownership of the study data.

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

3. At the completion of the study, PEDIG will distribute a final dataset to the Company for its needs regarding FDA submission (as a general rule, PEDIG 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 PEDIG in writing.

C. Publications, Presentations, and Publicity

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

2. PEDIG will provide the Company 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 PEDIG and the Company agree on different time intervals, the Company will be given 14 days to comment on manuscripts and abstracts and up to an additional 30 days if there is a need for the Company to submit patent application materials to obtain patent protection.

3. PEDIG will have the opportunity to review and must approve all press releases of the Company related to the study prior to their release.

4. The Company may not publish, present, or otherwise release any study results or information about the study that have not already been publicly disseminated by PEDIG.

D. Data Integrity

1. The PEDIG Coordinating Center will oversee data collection, data cleaning, data lock, data maintenance, etc. PEDIG utilizes electronic data capture as the source documentation for most data. PEDIG will provide the Company with details of these procedures for the Company to verify that these procedures meet regulatory requirements.

2. The Company may conduct a yearly site visit of the PEDIG Coordinating Center to evaluate database maintenance and other Coordinating Center procedures as they pertain to meeting regulatory requirements.

E. Clinical Sites

1. With input from the Company, PEDIG will select the participating sites.

2. PEDIG will establish the procedures for site certification and be responsible for certification of the sites. Certification includes the review and approval of regulatory documents such that the clinical site is approved to receive investigational product and subsequently enroll patients. The Company may review these procedures to verify that they are in accord with regulatory requirements.

F. Site Monitoring

1. PEDIG will determine the monitoring needs it deems critical for the study and provide the support needed for such monitoring. The Company may review the PEDIG site-monitoring plan to verify that it meets regulatory requirements.

2. If the Company determines that additional monitoring is needed for regulatory purposes, PEDIG will consider this request but will have the right to reject the request. Support for any additional monitoring will be provided by the Company.

3. Site monitoring will be overseen by the PEDIG Coordinating Center, which will have the option of conducting this monitoring itself.

4. The Company will not be permitted to contact the clinical sites, request data, or conduct monitoring visits without approval from PEDIG. Permission may be granted in the event of a pending FDA audit.

G. Adverse Event Reporting

1. PEDIG will establish a system for adverse event reporting, review, and coding. The Company may review this plan to verify that it is in accord with regulatory requirements and will meet the Company's needs for its FDA submission.

H. Efficacy and Safety Reviews, and Stopping Decisions

1. PEDIG will be responsible for developing the statistical analysis plan. The Company may review this plan to verify that it is in accord with regulatory requirements and will meet the Company's needs for its FDA submission.

2. An independent Data and Safety Monitoring Committee (DSMC) will review all data as appropriate and make recommendations to PEDIG regarding protocol modifications and stopping a study for efficacy or safety. The Company will not be provided with the study data until either the end of the study or the DSMC's decision that such data can be provided.

3. PEDIG will provide the Company with monitoring reports related to study progress (e.g., recruitment, protocol deviations, and retention reports).

I. Investigational Product

1. The Company will be responsible for providing the investigational product, placebos (when applicable), packaging of the investigational product, and all necessary manufacturing information for preparation of the IND or IDE and any related materials. The Company will agree to provide the investigational product and related materials for the duration of the study.

2. Investigational drug will be manufactured in accordance with Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) standards. Investigational devices will be manufactured in accordance with GMP standards.

3. PEDIG will develop procedures for supplying the investigational product to the clinical sites, maintaining accountability of the investigational product at the site, and disposal or return of the investigational product. The Company will pay for the costs of a pharmacy to store and ship the investigational product, supplying investigational product to the clinical sites and returning investigational product for disposal, if required. At the Company's request, PEDIG will consider allowing the Company to supply the investigational product and related materials directly to the clinical sites.

4. For device studies, the Company will provide technical support for the duration of the study.

J. Laboratory Measurements

1. In collaboration with the Company, PEDIG will determine those laboratory measures it deems necessary for the study and the selection of a central laboratory.

2. The Company may identify additional laboratory measures required for regulatory or other purposes. PEDIG will attempt to accommodate these needs as long as they do not adversely affect the conduct, data validity, or safety of the study.

K. FDA Registration and Submission

1. PEDIG will hold the IND or IDE for the study, unless agreed upon otherwise with the Company.

2. The Company will be responsible for performing registration and submission-specific analyses and preparation as needed.

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

L. PEDIG Policies

1. The Company will be provided with a copy of PEDIG policies and the Terms and Conditions of the NEI Cooperative Agreement.

M. Study Committees and Oversight

1. The Company may appoint an individual to serve as the Company liaison to PEDIG.

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

N. Legal Agreements

1. A legal agreement will be established between the Company and the Jaeb Center. The legal agreement will contain an indemnification section that specifies the situations in which the Company will provide indemnification, a confidentiality section agreeable to both parties, and an intellectual property section agreeable to both parties.

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

O. Cost Sharing

1. PEDIG through its NIH grant may provide funding for studies that are associated with:
   - one definitive efficacy trial per specific intervention that meets PEDIG standards
   - earlier stage trials (e.g., dose ranging) or other trial designs as deemed appropriate by PEDIG

2. When study costs are shared between PEDIG and the Company, PEDIG typically will cover the costs of the Coordinating Center and other infrastructure costs (except for those explicitly excluded in #3 and #4 below).

3. PEDIG will usually not support clinical trial costs that are:
   - Not necessary for optimal academic clinical trial design and implementation (e.g., additional monitoring, special laboratory analyses, etc.)
   - Associated with additional patient numbers required by the Company (e.g., to have enough power to analyze data as two definitive trials according to FDA guidance) or to conduct a second parallel trial.

4. In general, the Company 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 investigational product and any other related costs associated with the intervention
    - 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 PEDIG would be typically performing
    - All costs involved related to FDA and other regulatory agencies
    - All costs involved for pharmacokinetic study or other preclinical or ancillary studies mutually agreed upon by PEDIG and the Company