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Chapter 11: Study Policies

11.1 Identifying Risk and Reporting for CITT

All risks are the same for this study as they would be for non-participating subjects receiving VT/Orthoptics or pencil push-up treatment. Risks include a potential temporary increase in symptoms such as eye discomfort, eyestrain, mild to moderate headaches, blurred vision, intermittent or transient diplopia, sleepiness, difficulty concentrating, movement of print and loss of comprehension of read material after short periods of time. Time lost during non-productive treatment may also be included. The likelihood that these potential side effects would occur any more often within the constraints of the CITT than they would in the context of care obtained outside the CITT are the same.

Subjects in all treatment groups will be monitored weekly during the treatment phase for any adverse events (AE). Upon the occurrence of any adverse event, as defined in section 11.1.1, the following steps must be taken:

1. An intervention must be provided by the unmasked examiner or the principal investigator at the clinical site.
2. Within 24 hours, the Adverse Event Form, (see Appendix) must be completed by the principal investigator and faxed to the Data Coordinating Center and also to the Study Chairman's office.
3. If applicable, the principal investigator must report the event to his /her IRB (see guidelines below).

11.1.1 DHHS Adverse Event (AE) Reporting Guidelines

DHHS (Department of Health and Human Services) regulations [45 CFR 46.103(b)(5)] require institutions to have "written procedures for insuring the prompt reporting to the Institutional Review Board (IRB), appropriate institutional officials, and federal departments or agencies, any *unanticipated* problems involving risks to human subjects or others." These problems are frequently referred to as **ADVERSE EVENTS** (defined below). Because the IRB is responsible for the continued assessment of the risks versus benefits of research involving human subjects, investigators are required to notify the IRB of any adverse event fulfilling the following criteria:

1. The adverse event is **SERIOUS** (as defined below),
Or
2. The adverse event is not serious, but is **UNEXPECTED** and its association with the research-related procedure is either **DEFINITELY, PROBABLY, or POSSIBLY RELATED**, or **UNKNOWN** (as defined below).

11.1.1.1 DHHS AE Definitions

Adverse Event: Any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure; also an "unanticipated problem" of any nature (e.g., psychological or social

harm) (designated as unrelated, definitely related, probably or possible related) (see definitions below).

Serious adverse event: Any adverse event that is fatal or life threatening, is permanently disabling, requires subject hospitalization or prolongs hospitalization, or results in a congenital anomaly or birth defect.

Life-threatening event: Any adverse event in which the subject is at immediate risk of death from the reaction as it occurs; does not include a reaction that, if it were to occur in a more serious form, might cause death.

Unexpected event: Any adverse event that is not identified in nature, severity, or frequency in the investigational brochure, study protocol, consent form, or IRB application; or the event was more serious than anticipated.

11.1.1.2 DHHS AE Associations

Definitely Related: An adverse event that has a timely relationship to the administration of the investigation procedure and follows a known pattern of response for which no alternative cause is present.

Probably Related: An adverse event that has a timely relationship to the administration of the investigation procedure and follows a known pattern of response, but for which a potential alternative cause may be present.

Possibly Related: An adverse event that has a timely relationship to the administration of the investigation procedure, and follows no known pattern of response, but a potential alternative cause does not exist.

Unrelated: An adverse event for which there is evidence that it is definitely related to a cause other than the investigation procedure; in general, no timely relationship to the administration of the procedure exists, or if so, the event does not follow a pattern of response and an alternative cause is present.

The adverse event policy is not limited to adverse events resulting from investigation involving drugs, but also includes AE's involving any investigational device or research related procedure. Federal policy [45 CFR 46.116(b) (5)] also requires that investigators inform subjects of any important new information that might affect their willingness to continue participating in the research. The IRB should receive copies of any such information conveyed to subjects. When an adverse event necessitates changes to the consent/assent form(s) and/or protocol, that notification is given to currently or previously enrolled subjects, an amendment request should be submitted in conjunction with the adverse event report. The IRB will make a determination whether any new findings, new knowledge, or adverse events should be communicated to subjects.

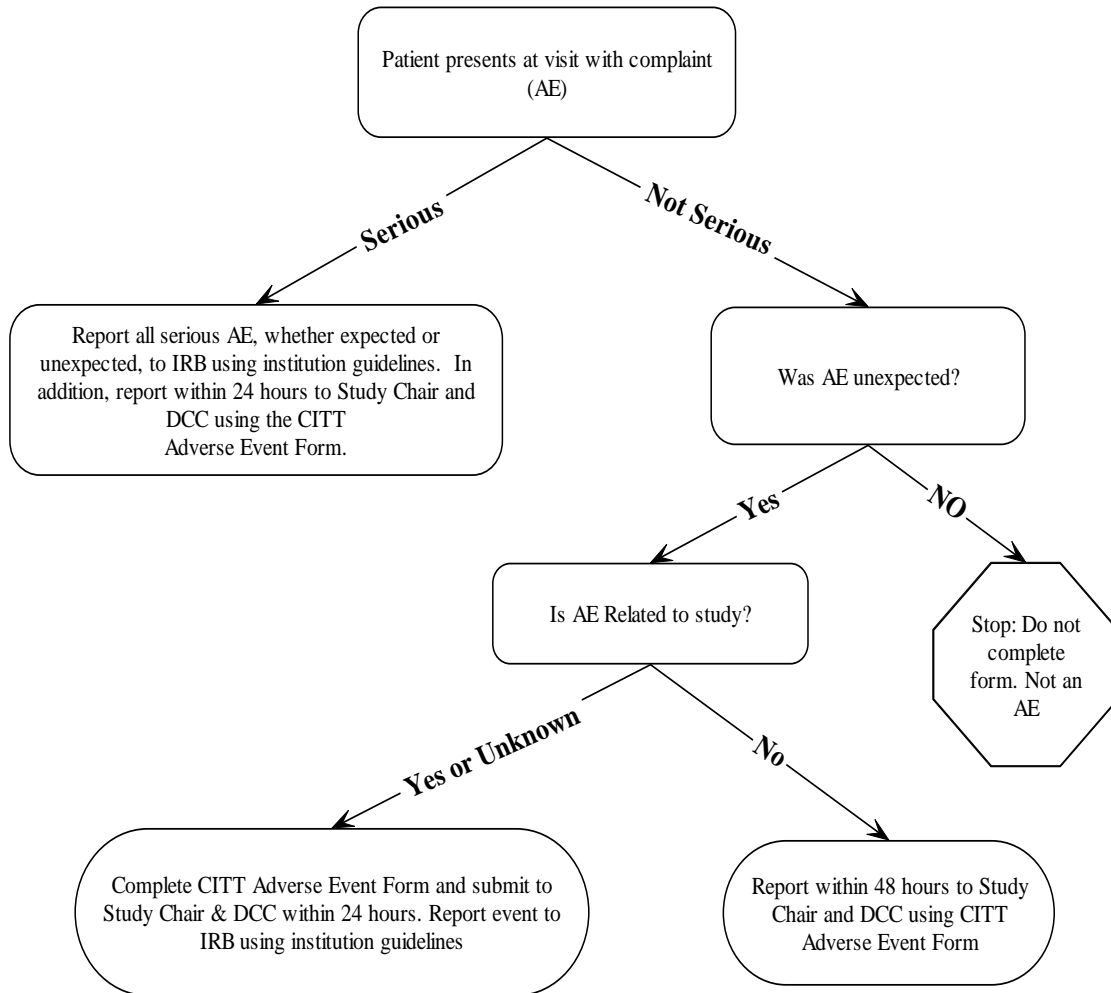
Although there is no universally accepted time requirement for reporting adverse events to the IRB, serious adverse events should be reported within 10 days of learning of the event. If the adverse event involved the death of a subject enrolled by an investigator, it should be reported immediately, usually within 72 hours. Note: deaths from "natural causes" or underlying disease that occur more than 30 days following completion of study interventions (i.e. events not temporally associated) need not be reported. Unexpected adverse events that are not serious but

may be associated with the procedure (see below) should be generally reported to the IRB within 30 days of notification of the event.

In some instances, adverse events or “unanticipated problems” result in social or psychological harm rather than physical harm to subjects or others. These events should also be reported to the IRB within 30 days, unless they are considered “serious”. A letter format may be used for reporting these events instead of the Adverse Event Reporting Form, as applicable.

Each Clinic Site will be required to follow its institution’s policy in regards to reporting AE’s to its Research Risk Protection Board located within its IRB facility.

11.1.2 Adverse Event Flowchart



11.2 Publicity

All publicity and press releases require prior approval of the Executive Committee and the local IRBs. Study investigators who are approached by the press for information concerning the study should refer these inquiries to the Study Chair.

11.3 Publication and Presentation Policy

11.3.1 Publication of Primary Study Design, Methods and Findings

The Executive Committee establishes writing committees for generating scientific publications emanating from the design and data collection of the CITT study. The committee will review and approve all topics for manuscripts. Investigators may volunteer for writing assignments and suggest additional topics where appropriate. A representative of the DCC will be appointed to writing committees on papers or presentations requiring study data.

Main outcome publications will list the CITT Study Group as author, with an acknowledgement to the writing committee. All professional participants past and present of CITT will be listed at the end of each paper and are considered as contributors.

All main outcome publications and presentations must receive approval of the Data and Safety Monitoring Committee prior to submission to any professional journal or presentation at a meeting.

New NIH (National Institutes of Health) policy guidelines for accelerated public access to published articles must be followed. The policy request that NIH-funded scientist submit an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part by NIH for public access be made as soon as possible, and within 12 months of final publication.

Each publication must acknowledge the National Eye Institute support as follows: "Supported by grants from the National Eye Institute, National Institutes of Health, and Department of Health and Human Services."

Reprints of published papers will be mailed to each CITT Clinic Site for distribution among personnel. Five reprints of each paper are sent to the Study Chair for the CITT Library.

11.3.2 Publication of Secondary Manuscripts

The investigator should submit an abstract and a short description of the proposed paper including co-authors, data to be reported and timelines for drafts and submission to the Executive Committee for approval. This review process is intended to ensure the quality of publications and to refine the proposal. Requests to publish results on primary and secondary outcomes from data pertaining to single or several clinic sites will not be considered by the EC until after the publication of the major CITT study report(s). The DCC is responsible for maintaining a database that tracks proposed and approved study publications and presentations. A list of

approved study publications and presentations will be distributed to all CITT investigators on a regular basis. Interested CITT investigators are invited to contact the primary author to add their name to the writing group. Should the workload associated with the preparation of papers exceed the resources of the DCC, it will be the responsibility of the DCC in conjunction with the Executive Committee to establish priorities. Upon approval of the proposed paper/presentation, a detailed analysis plan and timetable will be developed with the DCC. It will be the responsibility of the DCC to contact primary authors when timelines are not met. Major problems in the preparation of manuscripts will be referred to the Executive Committee.

The Executive Committee resolves conflicts regarding authorship. General guidelines for authorship are active participation in the production of the manuscript or other important contribution. Authorship rights are not available for membership on a writing committee only. If the timeline for a paper has expired with no substantial evidence of progress, authorship rights are assumed to have expired. The Study Chair will contact the primary author and leadership will be negotiated. The Executive Committee will be informed of changes in lead authorship. An individual may be given an acknowledgement for reading and providing comments on a manuscript.

The primary author and the DCC are responsible for coordinating all activities related to the writing and submission of papers and abstracts. The primary author will discuss analytic plans with the DCC, assign writing responsibilities to co-authors, meet timelines, determine the order of authorship, and circulate drafts to co-authors. The DCC is responsible for arranging conference calls and circulating final drafts (before submission for publication) to 1) all participating CITT Investigators, 2) all members of the Executive Committee, and 3) the Data and Safety Monitoring Committee. Upon circulation of the draft, there will be a two-week period during which members can make comments about the paper.

New NIH (National Institutes of Health) policy guidelines for accelerated public access to published articles must be followed. The policy request that NIH-funded scientist submit an electronic version of the author's final manuscript, upon acceptance for publication, resulting from research supported in whole or in part by NIH for public access be made as soon as possible, and within 12 months of final publication.

Each publication must acknowledge the National Eye Institute support as follows: "Supported by grants from the National Eye Institute, National Institutes of Health, and Department of Health and Human Services."

Secondary outcome publications will be distributed to the DSMC for informational purposes.

11.3.3 Presentations

The Executive Committee must approve oral presentations and abstracts in advance of submission. No unpublished CITT results may be used for oral presentation, local or otherwise without the consent of the Executive Committee. Study results include all data collected for the CITT. The above restrictions do not apply to local presentations of the design of CITT, provided

that these presentations contain no unpublished study results. Such presentations are encouraged to stimulate subject recruitment.

11.3.4 Publications from Ancillary Studies

All ancillary studies must first be approved by the Executive Committee and the DSMC before they are begun (see Section 11.4). Manuscripts dealing with ancillary studies carried out in conjunction with the CITT must be sent to the Executive Committee for review and approval before submission for publication. In addition, the manuscript must also be sent to the DSMC for review and approval if they decided to monitor the ancillary study for safety reasons. Investigators may not independently use study data collected at their clinic.

11.3.5 Publications Concerning Methodology

The Executive Committee encourages the investigators to publish methods employed to carry out CITT functions and topics related to research methodology. For example, these publications may deal with methods used for data management, statistical analysis, quality assurance, or other procedures.

Review and approval by the Executive Committee are required before the manuscripts concerning methodology are submitted for publication. The DCC is responsible for distributing copies of methodological publications to the Executive Committee, DSMC, and other CITT investigators. Five reprints of all such publications should be sent to the Study Chair for the CITT Library.

11.4 Ancillary Study Policies

Individual investigators may propose ancillary studies. However, to protect the integrity of the CITT, ancillary studies must be reviewed and approved by the CITT Executive Committee and the DSMC before their inception.

No additional testing or measurements for research purposes can be made on CITT subjects without prior approval of the Executive Committee and the DSMC. The DCC will collaborate with the ancillary study investigators on data analysis if the CITT data is required.

11.4.1 Definition of an Ancillary Study

An ancillary study is a research project that requires either:

1. Supplemental observations or procedures to be performed on any CITT subject according to a set protocol OR
2. Additional work to be done by or information to be obtained from the DCC.

11.4.2 Rationale for Approval Requirement

Everyone involved in CITT is entitled to prior assurance that no ancillary study will:

1. Complicate the interpretation of CITT results

2. Adversely affect subject cooperation or recruitment
3. Jeopardize the public image of the study
4. Create a serious diversion of study resources, locally or at the Data Coordinating Center

11.4.3 Preparation for Approval Request for Ancillary Study

The request for approval of an ancillary study requires two steps. The first step is a brief description of the proposed study in narrative form stating the primary hypothesis and a brief description of the study. This is sent to the Study Chair and reviewed by the Executive Committee within one month of receipt. If approved for further consideration, a detailed description should be submitted in narrative form following the standard PHS 398 format and must provide information on the additional subject burden imposed by the ancillary study, informed consent procedure, extra time, extra visits, etc.

If access to CITT data is required, the investigator must specify what data are needed and a timetable for access to such data. Access to CITT data requires approval from the Executive Committee.

All ancillary studies must have local IRB approval for all CITT clinic sites and resource centers involved.

11.4.4 Publication of Ancillary Study Results

All manuscripts based on ancillary study data must be reviewed and approved by the Executive Committee and the DSMC (if the DSMC is monitoring the ancillary study for safety) before publication or presentation.

11.5 Access to Study Information

11.5.1 Study Documents

The CITT Manual of Procedures and copies of data collection forms used in CITT will be placed in a suitable repository, such as that maintained by the National Technical Information Service, for access by any interested party. These documents may be referenced without prior approval once they have been placed in the repository. The DCC Principal Investigator replaces documents in the archives with updated copies whenever substantive changes are made in the procedures or methods, as determined by either the Executive Committee or the Data and Safety Monitoring Committee.

In general, the following documents may not be released to any group or individual outside the CITT Study Group:

1. Minutes of CITT meetings
2. Performance monitoring reports for CITT Clinics
3. Data and Safety Monitoring Committee reports

11.5.2 CITT Study Data

Access to CITT data on individual subjects is prohibited to unauthorized persons, whether on file in a clinic or in the DCC. The identity of individual CITT subjects may not be revealed in any public report or presentation.

Chapter 11 Appendix

Convergence Insufficiency Treatment Trial
ADVERSE EVENT FORM

- -
SUBJECT ID

DATE FORM COMPLETED - -

DATE OF EVENT - -

Adverse Event Serious AE Life-Threat AE Unexpected AE

Description of adverse event _____

Treatment prescribed _____

Related to treatment?

Definitely Related Probably Related Possibly Related Unrelated

Examiner