STUDY PROCEDURES MANUAL (SPM)

Proton Collaborative Group Protocol BRE008-12

Phase II Study of Postoperative, Cardiac-Sparing Proton Radiotherapy for Patients with Stage II/III, Loco-Regional, Non-Metastatic Breast Cancer Requiring Whole Breast of Chest Wall Irradiation with Lymph Node Irradiation

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CONTACT INFORMATION FOR SPONSOR REPRESENTATIVES

Study Representative	Contact
Study Chair Responsible for complete oversight of the study. Specific tasks include: all protocol and safety monitoring of the study, coverage to answer all questions related to AEs, reviews and evaluates study data relevant to the safety of the regimen and for monitoring and evaluating all SAEs in consultation with the site investigator and PCG Data Safety Monitoring Board.	Eugen Hug MD Telephone (cell): 908-938-4684 Email: eugen.hug@procure.com
Proton Collaborative Group (PCG) Responsible for training, monitoring and oversight of study sites to ensure the study is conducted according to the written protocol and is in compliance with PCG Policies and Procedures, applicable site Policies and Procedures, GCP, and FDA regulations. ***Contact PCG for urgent reporting***	E-mail: hq@pcgresearch.org
Data Manager Responsible for monitoring data compliance and data validation	PCG Data Management Telephone (cell): 405-249-0583 E-mail: hq@pcgresearch.org

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1.0 GENERAL INFORMATION

1.1 Overview of Manual

This document is confidential. It is to be used by PCG members only in conjunction with the PCG protocol. No other use or reproduction is authorized by the Study Chair nor does the Study Chair assume any responsibility for unauthorized use of this document.

This Study Procedures Manual (SPM) complements Protocol BRE008-12 by providing additional information and clarification about the following: how the clinical and administrative aspects of the study should be conducted to aid in ensuring compliance with the protocol, the principals of Good Clinical Practice (GCP), all applicable federal regulations and Proton Collaborative Group (PCG) requirements.

All individuals who are responsible for conducting Protocol BRE008-12 should refer to this SPM in conjunction with the protocol.

1.2 Manual Revisions

A copy of the SPM will be issued to the study site at or prior to the site initiation. If revisions to the SPM become necessary, the revised SPM, with the revision date on the front cover, will be distributed to the study site(s).

The investigative site will be responsible for placing the revised SPM in the investigator's study files and utilizing the current SPM.

1.3 Regulatory Procedures

This study must be conducted according to applicable regulations stated in title 21 of the United States Code of Federal Regulations (CFR) and the ICH Good Clinical Practice (GCP): Consolidated Guideline (ICH E6). Additional requirements are also outlined in protocol.

As specified in ICH E6, sections 4.9 and 8, the investigator is responsible for retaining all study-related documentation.

The study site's regulatory documents must be current with PCG prior to participation in this study and maintained as required throughout the study. This study will be conducted only at institutions who are members of PCG. The respective local institutional review board (IRB), independent ethics committee (IEC), or central IRB must be used during this study to grant approval for research conduct at each site. The BRE008-12 protocol has been approved as a multi-site study through Western IRB (WIRB). Sites that are not obligated to use a local IRB may submit the study to the WIRB using their short form process.

If needed per site or IRB requirements, a complete CRF template packet is available by contacting HQ@pcgresearch.org or your PCG Study Monitor.

Samples of forms to meet regulatory requirements, such as Delegation Log and Subject Identification List are available at: www.pcgresearch.org under Forms. When utlizing these templates, the original should be maintained, and updates should be made the original to maintain legibility of the document after multiple changes.

1.4 Investigator Responsibilities

The site Principal Investigator (PI) is responsible for all aspects of the clinical research protocol being conducted at their site. For those protocols that involve chemotherapy and/or surgical intervention, the PI must work closely with their designated medical oncologist or surgeon to assure protocol compliance and protection of human research subjects. It is highly recommended that the site PI host a meeting with designated surgeon (s) or medical oncologist(s) to review the protocol prior to enrollment of subjects.

Protocol changes or amendments that may affect the modality must be circulated to allparticipating surgeons and/or medical oncologists at the institution.

If patient protocol compliance appears to be a problem, or if the protocol regimen will not be followed by the attending physician, the patient should not be entered into a study. Problems with treatment compliance or surgical or medical oncology data submission will be referred to the site PI for resolution. Problems that persist will be referred to the Study Chair.

1.5 General Research Considerations/Expectations

Revisions to paper or electronic documents (source, regulatory and/or Case Report Forms) must follow acceptable guidelines:

- Original electronic or paper documentation must be maintained.
- Be sure the revisions are clearly identifiable in either or electronic records. On paper documents, use a single line to cross through the information being changed, initialize the revision. You may circle the question or write on top of the page specific items that, have been revised.
- **Do not use whiteout or highlighter.**

Laboratory results must be reported in US equivalents unless otherwise specified.

All source documents including required reports: (e.g., pathology, surgery) must be in English.

1.6 Monitoring Procedures

In order to assure data integrity for the BRE 008-12 protocol, sites will be monitored following the PCG clinical trial monitoring SOPs by the PCG Study Monitor or other applicable PCG staff.

Prior to the first subject enrollment, the PCG Study Monitor or other assigned PCG staff will conduct a site initiation visit. This may be done in person or via teleconference. It is expected that the site research staff will have read the protocol prior to this meeting. The goal of this meeting is to assure site staff are qualified and prepared to comply with the protocol and all related study procedures.

Each site participating in this study will be subject to remote monitoring every three months. Monitoring will be conducted by a member of the PCG staff and will include the following:

- A full source verification of 10% of all active study patients at that site

- A 100% source verification for critical data as defined by the August 2013 Food and Drug Administration Guidance for Industry: Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring.
    - Verification that informed consent was obtained properly
    - Adherence to protocol eligibility
    - Source verification and review of all SAEs and any grade 3 or higher AE
    - Source verification for any treatment failures or deaths
- Review of the site regulatory files
- Review of any outstanding queries

Sites will also be subject to on-site monitoring or more frequent remote monitoring if issues are identified that could disrupt the integrity of the trial or compromise patient safety.

Sites will be notified by email one week in advance of each remote monitoring visit. Reports of all findings will be sent to the site's study staff, including the Principal Investigator, within one week of monitoring completion. The site will be responsible for addressing all finding prior to the start of the next monitoring visit for this study.

If there is any evidence of fraud discovered during an audit, PCG will notify the Group Chair. The institutional's accrual may be suspended until appropriate action can be taken, including a second site visit for a comprehensive review of all enrolled subjects. If fraud is confirmed, the institutions membership may be terminated and notice will be send to the applicable IRB.

2.0 SCHEDULE OF EVENTS

2.1 On Treatment

The study will be conducted on an outpatient basis, according to the schedule of time and events provided in Protocol BRE008-12.

2.2 During Follow Up

In order to assure subject safety and integrity of the study, follow-up visits should be completed per the schedule of time and events in the BRE008-12 protocol. However, PCG allows the below windows for completion of follow up visits, as indicated below. If follow up visit are missed or completed outside of these windows, you will be required to complete a Deviation Report Form (see section 4.2).

- 4-8 week follow-up visit – no window
- 6 months & then annual follow-up visits: +/-30 day window
- If you can confirm that the subject will not return for follow-up visits, alert PCG and make every effort to obtain data from the subjects' referring physician

3.0 ELIGIBILITY AND ENROLLMENT

3.1 Informed Consent

Informed consent must be obtained from subjects before they can be enrolled in the study as specified in 21 CFR 50 (Protection of Human Subjects) and ICH E6 Section 4.8. The subject must sign the IRB approved consent form. In the Food and Drug Administration

Information Sheets dated September 1998, the following specifications are made and adopted by PCG as policy:

Procedures that are to be performed as part of the practice of medicine and which would be done whether or not study entry was contemplated, such as diagnosis or treatment of disease or medical condition, may be performed and the results subsequently used for determining study eligibility without first obtaining consent. On the other hand, informed consent must be obtained prior to initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for research. When a doctor-patient relationship exists, prospective subjects may not realize that clinical tests performed solely for determining eligibility for research enrollment are not required for their medical care. Physician-Investigators should take extra care to clarify with their patient-subjects why certain tests are being conducted.

In addition, in the United States each subject must sign and date the authorization for use and disclosure of protected health information (PHI) under the Health Insurance Portability and Accountability Act (HIPAA) before the investigational site can transmit any PHI. Note that it is acceptable to combine the informed consent with the HIPAA authorization; in this case, only a single signature and date is required.

3.2 Subject Registration

Refer to the the protocol for information required prior to patient registration (in addition, an optional Eligibility Worksheet is included in Appendix I). Once the investigator verifies a subject's eligibility, the subject will be registered in the Proton Collaborative Group electronic data collection (EDC) system. (Guidance documents for the registration process are available at: www.pcgresearch.org under Forms).

Upon entering a new eligible subject into PCG EDC, a unique patient identification number will be assigned. The first three digits represent the site number. The last four digits are assigned sequentially for patients enrolled at the site. The subject identification number (i.e. subject # 002-0001) will be used for the remainder of the study to identify the enrolled subject.

3.3 Investigator Refusal

An investigator should not enroll patients in a study unless s/he has reviewed the protocol and agrees to accept all of the study treatment options if randomization applies. Failure to accept an assigned option may result in suspension of the investigator from further enrollment in the study.

3.4 Patient Refusal

All treatment options in a study must be explained to potential study participants and the role of randomization explained, if applicable. If a patient changes his/her mind and is unwilling to start or continue with the assigned option, PCG should be notified in writing. Follow-up should continue to be submitted according to schedule unless patient withdraws consenet. Please see section 6.0 for additional information on subject withdrawal. Once enrolled in a study, the patient does need to be accounted for so that accumulation of delinquent data by the institution will not occur.

4.0 PROTOCOL EXCEPTIONS AND DEVIATIONS

4.1 Protocol Exceptions

No protocol exceptions will be granted for this study. Contact the PCG Study Monitor for any questions regarding eligibility.

4.2 Protocol Deviations

It is expected that the protocol will be followed without variation. However, if a protocol procedure is not completed according to the protocol, a Deviation Report Form must be completed upon discovery and sent to the PCG Study Monitor (form is available at: www.pcgresearch.org under Forms).

If the site is aware that a deviation will occur, for example if a patient refuses to return to the office for follow-up but is willing to complete visit assessments by phone, the site can request that the Study Chair grant a planned deviation Note to File. This will be kept in the site's regulatory file as well in PCG's Trial Master File.

5.0 DATA SAFETY MONITORING

Data will be reviewed by the PCG Data Safety Monitoring Board, as required per the protocol. A summary of this report will be sent to participating sites for submission to their IRB if required.

6.0 SUBJECT WITHDRAW GUIDELINES

All treatment options in a study must be explained to potential study participants and the role of randomization explained, if applicable. **If a patient changes his/her mind and is unwilling to start or continue with the assigned option, notify the PCG Study Monitor and/or PCG headquarters (HQ) in writing. Follow-up should continue to be submitted according to schedule unless directed otherwise by PCG HQ**. Once enrolled in a study, the patient will need to be accounted for in the analysis; therefore, it is important to obtain an agreement from the patient to be followed so that accumulation of delinquent data by the institution will not occur.

Subjects may choose to withdraw from a study at any time. There are two scenarios for withdrawal: 1) withdrawal from study only or 2) withdrawal from study AND withdrawal of consent. The medical and study record must reflect the specific wishes of the subject and the following procedures should be followed:

a) **Subject withdraws from study but does NOT withdraw consent. For example, subject may not want to continue prescribed treatment, he/she does not wish to follow all protocol assessment, or he/she does not want to participate in follow-up visits, etc. However, consent remains in place to allow for continued use of data collection and use for research.** If the patient decides to discontinue follow-up with the PCG investigator, this too is acceptable; however, a process to obtain information from other sources should be discussed, i.e. release of information by other sources, etc. If this is not acceptable to the patient, the investigator should encourage the patient and request permission to submit survival status data. Although the patient has the right to refuse submission of all data, she/he should be informed that failure to provide survival status and information about treatment toxicity may adversely affect the study results. A "release of information" document may need to be signed by the patient. Consult institutional policy regarding this process. The policy and duration of the release may differ among institutions.

b) Patient withdraws from the study AND withdraws consent. This must be documented in writing. This document must then be forwarded to PCG. Per regulations, information that has previously been collected may still be used but no new information will be gathered or used.

7.0 SUBJECT LOST TO FOLLOW-UP

Subjects will be categorized as "lost to follow-up" only after **at least** 6 attempts to contact subject/obtain information have been attempted over a period of at least 12 months. Documentation of efforts should be maintained in the subjects' records. If unable to contact patient directly consider contacting other medical providers, local cancer registry and/or social security death index.

The PI of an institution with frequent occurrences of lost patients may be requested to submit a Corrective Action Plan (CAP) in writing with an assessment of the reason(s) for the problem and a plan to avoid additional lost to follow-up occurrences.

8.0 TRANSFER SUBJECT TO ANOTHER FACILITY

To transfer a protocol patient to another PCG institution with protocol approval, the investigator who originally enrolled the patient must submit a written request to the PCG Study Monitor and/or PCG HQ via the Patient Transfer Form, available at www.pcgresearch.org under Forms.

Issues related to medical insurance are the responsibility of the investigators involved in the case transfer. All delinquent data through the date of transfer should have been resolved before the transfer. Subsequent to case transfer, responsibility for all data requests and data submission is transferred to the recipient investigator including institutional requirements.

Transfer of cases from a PCG member institution to a member of a different cooperative group or transfer of a case from another cooperative group to a PCG member institution cannot be made.

9.0 DATA ENTRY

9.1 PCG Electronic Data Capture System

For instructional guidance on how to log in, update password, register patients and enter data utilizing the PCG EDC System, please access guidance documents at: www.pcgresearch.org under Forms.

9.2 Data Submission Schedule

Data should be submitted in a timely manner to assure subject safety and meet high data integrity standards. As per PCG Policy, sites will be periodically evaluated for continued membership; timely data submissions are part of that evaluation.

CRF	**Due for completion:**
Demographic Form	Within 72 hours of study entry
On Study Forms	Within 72 hours of study entry
QOL Forms	Within 72 hours of study entry; Within 2 weeks of each applicable follow-up visit.
Cosmesis Forms (not for chest wall patients)	Within 72 hours of study entry; Within 72 hours of each follow-up visit
Breast Photographs	Within 72 hours of study entry; Within 72 hours of each weekly assessment; Within 72 hours of each follow-up visit

Acute Skin Reaction Assessment	Within 5 days of each weekly assessment; Within 5 days of the 4-8 week follow-up visit and the 6 month follow-up
Late Skin Toxicty Form	Within 1week of each follow-up visit
End of Treatment Form	Within 1week of treatment completion
Adverse Events Form	Within 1week of baseline, end of treatment and with each follow up visit, if applicable
Follow-up Form	Within 1week s of each follow up visit
Autopsy Report	Within 1week of event, as applicable
SAE Form	Within 1 business day, as applicable (see adverse events section of the protocol for more information)

* Autopsy reports should be scanned and emailed or copied and mailed to PCG HQ. They must be de-identified by completely marking out the patient's name and any other identifiers. The study subject number and subject's initials should be written in on the document.

9.3 Quality of Life Forms Data

Ideally, subjects should complete the Quality of Life forms on their own. If the patient cannot complete the form on their own, they should be given assistance to complete the form either at the time of their clinic visit or with assistance over the phone. Please note that there are two versions of this form: one specific to post mastectomy patients and one specific to lumpectomy patients. Please ensure the proper form is used.

Patients should be instructed to read the brief directions at the top of the page. After it has been confirmed that the patient understands the directions, patients should be encouraged to answer all items, in order, without skipping any. If the patient feels an item does not apply to him/her, he/she should be encouraged to choose the response that is the most applicable. Patients should complete the questionnaires without coaching by staff. Once completed, research staff should verify that every item has been answered and remind the patient to answer any questions that were missed. If the patient declines to respond to any item, or the entire form, staff should document an explanatory response in the patient's medical/source record.

It is important to note that the QOL forms are utilized to collect patient reported outcomes whereby physician and nurse assessments and documentation are a separate research data source. Staff should not try to cross reference the information given on the QOL forms with their own assessment of the patient's condition. The answers on the QOL forms should not be used to "quiz" the patient but rather kept as confidential as possible in order to avoid influencing the patient responses. The information provided by the patient in the completed questionnaires is confidential and should not be discussed with, or shown to, anyone who is not a member of the study team.

For the BRE008-12 study the patient-completed quality of life questionnaire will be administered at baseline, after informed consent has been obtained and last surgery, but prior to start of radiation treatment. It will be administered again at the 6 month follow up, 1 year after completion of radiation, and then annually for 5 years. Patients who experience a breast cancer recurrence or second primary cancer will not be expected to complete the QOL form. Patients who discontinue protocol therapy for other reasons will be expected to continue the assessments on schedule. All QOL forms must be entered into PCG's EDC system. Skipped or missing forms must also be accounted for in the EDC system. The QOL questionnaire should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaire is completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by

mail or phone. For instructions for administering the QOL questionnaire, including details such as how to administer it over the phone, please contact PCG.

9.4 Cosmesis Instructions

The cosmesis questionnaire will be completed by the treating physician or nurse at baseline and then at each follow-up timepoint outlined in the protocol. This does NOT have to be done for chest wall patients. It can be completed by the radiation oncologist, the surgeon or the research nurse/coordinator. We strongly urge that all assessments be performed by the same individual. If a patient experiences a breast cancer recurrence or second primary cancer cosmesis assessments will not be expected. Patients who discontinue protocol therapy for other reasons will be expected to continue the assessments on schedule. All cosmesis forms must be entered into PCG's EDC system. Skipped or missing forms must also be accounted for in the EDC system.

9.5 Toxicity Assessment

The Acute Skin Reaction Assessment and Late Skin Toxicity Assessment will be completed on each patient per the timelines outlined in the protocol. These forms will be used to capture the CTCAE grading of any AEs seen weekly during treatment and at follow-up. These forms will also capture AEs using a grading criteria developed mainly by Memorial Sloan Kettering (MSK). This criteria was developed with the intent of providing more accurate AE assessment criteria, specific to patients undergoing radiation therapy. These forms will used to compare the two methods of assessment. Each group of assessments (CTCAE and MSK) will need to be completed simulanteously at each timepoint specified in the protocol.

9.6 Photograph Instructions

Digital images (photographs) will be taken of the treated and untreated breasts as outlined below:

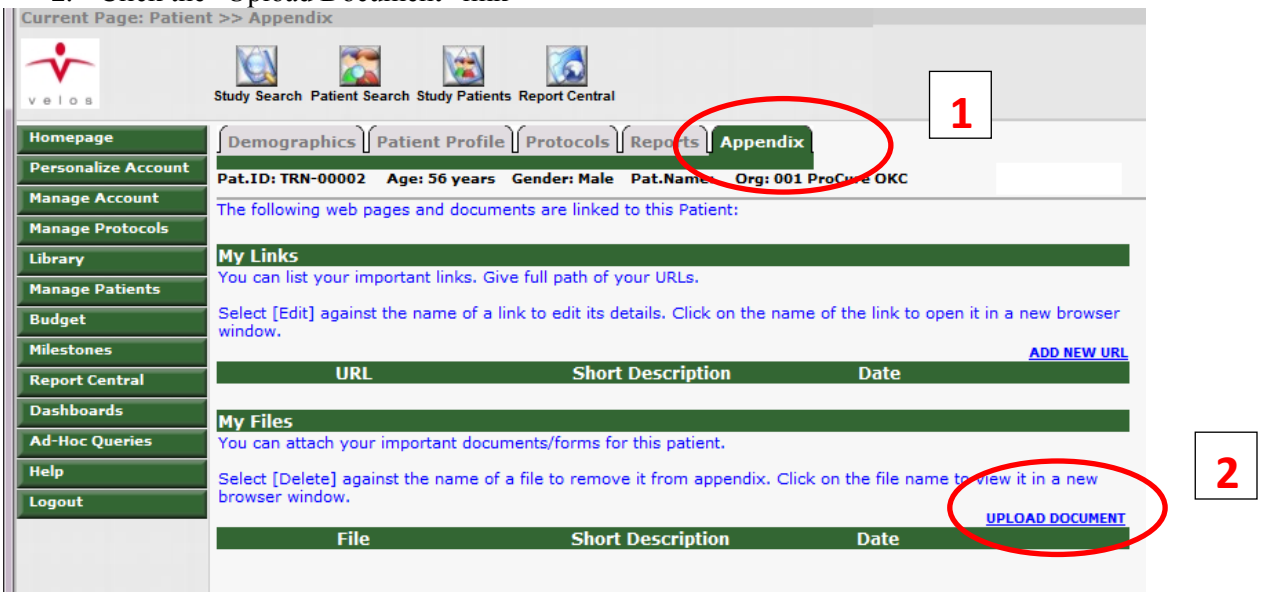
- Photographs of the patient in the treatment position with immobilization device in place at baseline.
- Weekly photographs of the patient to be taken during the on treatment visit for documentation of acute effects and subsequent correlation with cosmesis per the following guidelines.
- Photographs will be taken at each follow-up timepoint outlined in the protocol per the following guidelines.

Two digital images will be taken at each of the assessment points. One will be a close up of the treated breast alone in order to provide detailed information regarding the treatment effects.The second digital image will be a straight frontal view of both breasts taken in either a standing or seated position with the patient's hands symmetrically placed on her hips, taking care to exclude her face and framing or focusing on both the treated and untreated breast to allow optimal comparison of the breast for symmetry. At a mimimum, these two de-identified photographs will be submitted to PCG. Additional photographs may be submitted, per site discretion.

Digital photographs will be stored in the electronic data capture system, Velos, in each subject's specific file. Users will be required to enter the PCG patient ID number, image type, view type, time point, and the date photographs were taken.

Upload Process

1. After selecting a patient, select the patient Appendix at the top of the screen
2. Click the "Upload Document" link



3. Enter the date the photo was taken
4. The Short Description should be in the following format:
   a. XXX-XXXX_FML_V_T
      i. XXX-XXXX is the patient ID
      ii. FML is the patient initial. If a patient does not have a middle intial use "-"
      iii. V is view (S single breast close-upand B for bilateral frontal view)
      iv. T is for Timepoint (B for Baseline, 1 for 1-year, 3 for 3-year)
   b. Example: 001-0004_ABC_S_B

10.0 ADVERSE EVENT AND UNANTICPATED PROBLEM REPORTS

10.1 Adverse Event Reporting

Adverse event information related to protocol therapy will be collected in the EDC system according to protocol specifications.

10.2 Serious Adverse Event Reporting

If the subject experiences a Serious Adverse Event as defined by the protocol, a SAE Report Form must be completed and submitted to PCG via e-mail within one business day of when the investigator or site becomes aware of the event (SAE Report Form is available at www.pcgresearch.org). The SAE form must be updated and resubmitted when new information regarding the event is available.

In addition, adverse events meeting **all** of the following criteria must be reported to PCG by contacting the PCGPCG Study Monitor or PCG HQ within 5 working days of the time the investigator becomes aware of them:

- **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the subject population being studied; **and**
- **Related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the drugs, devices or procedures involved in the research); **and**
- Suggests that the research places **subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

The PCG Study Monitor or other designated PCG staff will determine additional steps and work with the site to complete the applicable documentation. As a reminder, sites are responsible for following the reporting requirements of AEs, SAEs, and unanticipated set forth per their own IRB policies and procedures since requirements may vary among IRB's. These reporting requirements may differ from those set forth by PCG. The severity of the AEs and SAEs will be graded using the CTACEv4 criteria.

10.3 Reporting Unanticipated Problems that ***are not*** Adverse Events

Investigators are to report Unanticipated Problems that fit the following criteria within 5 working days of becoming aware of them by contacting the PCG Study Monitor and/or PCG HQ:

- Unanticipated problems that do not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. For example, report occurrences of breaches of confidentiality, or accidental destruction of study records.
- **Unplanned** protocol deviations/violations that have already occurred, that may adversely affect *the rights, safety or welfare of subjects or the integrity*

of the research data, ***AND*** that meet the definition of an unanticipated problem (i.e., it involves risk to subjects or other people).

11.0 CENTRAL REVIEW OF TREATMENT PLANS

Per section 5.5 of the BRE008-12 protocol, the first 3 cases enrolled into the study at each site must be reviewed by a PCG Medical Physicist, the site Dosimetrist who completed the treatment plan and the Study Chair or designee, prior to start of treatment. Additional cases will undergo the same review process as determined/requested by PCG.

Once planning is approved, the Dosimetry Form will be signed by the site Dosimetrist, PCG Physicist representative, and Study Chair or Designee and then forwarded to the PCG Study Monitor.

12.0 NONCOMPLIANCE

Research sites that fail to comply with protocol, PCG policies/procedures, GCP and/or FDA regulations, may be subjected to develop and comply with a Corrective Action Plan to prevent future issues.

Continued or chronic noncompliance with protocol, policies/procedures, regulations or corrective action plans could result in study closure at the research center