Proton Collaborative Group

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ELECTRONIC DATA CAPTURE (EDC) INSTRUCTIONAL MANUAL

CONTACT INFORMATION FOR SPONSOR REPRESENTATIVES

Study Representative	Contact
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.	Email: HQ@pcgresearch.org Website: www.pcgresearch.org (EDC link is on the PCG website)
PCG Data Management Responsible for monitoring data compliance and data validation.	PCG Data Management Telephone: 405-757-4416 Email: HQ@pcgresearch.org

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2.2 Baseline Forms – Data collection on the primary disease being treated with radiation therapy. All data must be PRIOR to radiation start date.

- 2.2.1 (Initial) Diagnosis- information at the time the patient was diagnosed with cancer. In cases of recurrent disease, please pay attention to fields asking for "original" and "current" diagnosis information.
- 2.2.2 Prior Treatment- information on any treatment the patient had prior to radiation start (for the disease being treated with radiation therapy).
- 2.2.3 Baseline Parameters- information collected prior to radiation but after initial diagnosis.
- 2.2.4 Clinical and Pathological Staging (for applicable forms) ****NOTE:** All current categories of TNM staging are listed. If one is not listed, please review, as this may have been staged based on old criteria.
  - 2.2.4.1 Clinical staging definition per AJCC 7th edition- includes any information obtained about the extent of cancer before initiation of definitive treatment (surgery, systemic or radiation therapy, active surveillance, or palliative care) or within 4 months after the date of diagnosis, whichever is longer, as long as there is no systemic or radiation therapy initiated or the cancer has not clearly progressed during that time frame.
  - 2.2.4.2 Pathological staging definition per AJCC 7th edition- includes any information obtained about the extent of cancer through completion of definitive surgery as part of first course treatment or identified within 4 months after the date of diagnosis, whichever is longer, as long as there is no systemic or radiation therapy initiated or the cancer has not clearly progressed during that time frame.
  - 2.2.4.3 T=tumor— defined by the size or contiguous extension of the primary tumor
  - 2.2.4.4 N= regional node involvement— defined by the absence or presence and extent of cancer in the regional draining lymph nodes. Nodal involvement is categorized by the number of positive nodes and for certain cancer sites by the involvement of specific regional nodal groups
  - 2.2.4.5 M=metastases— defined by the absence or presence of distant spread or metastases, generally in locations to which the cancer spread by vascular channels, or by lymphatics beyond the nodes defined as "regional"
  - 2.2.4.6 Stage Grouping— Once the T, N and M are determined, they are combined for an overall stage of 0, I, II, III, IV.
  - 2.2.4.7 In the clinical setting, it is appropriate to combine clinical and pathological data when only partial information is available in either the pathological or clinical classification and this may be referred to as a working stage.

2.3 Adverse Events Forms – review EMR assessments, OTVs, Notes from RN/MD and so forth

2.3.1 Baseline / Pre-Tx Event - Collection of symptoms prior to start of radiation

2.3.1.1 Baseline Event would be stopped if it worsens or ends

2.3.2 Adverse Event - Collection of toxicities during radiation

2.3.2.1 Adverse Events are new symptoms or worsening of pre-existing symptoms during and/or after radiation treatment. So, if a symptom was present at baseline (or pre-treatment) it would be marked Baseline/ Pre-Tx. If the symptom (at the same grade) goes away and comes back during treatment, it is NOT an Adverse Event because it existed pre-treatment at the same grade. When the symptom is still the same grade during radiation it was at baseline, then the symptom was not affected by radiation. If the symptom comes back *at **a higher grade*****,** then it is an Adverse Event.

2.3.2.1.1 If source documentation clearly states that the baseline event returned *due to radiation*, please include a Note stating why categorized as an Adverse Event.

2.3.2.2 You may enter only the highest grade of each Adverse Event that occurs during radiation treatment. When an event starts/stops throughout treatment, use the first and last date the highest grade of the symptom was present. You do not have to enter every instance with start and stop dates. The Stop Date would be the end date of the last occurrence of the highest grade. However, it is NOT wrong to enter each instance.

2.3.3 Post Treatment Adverse Event – Collection of toxicities in follow-up

2.3.3.1 For Adverse Events that occur during follow-up, all instances need to be entered.

2.3.3.1.1 So, during treatment only the highest grade can be entered (example Grade 2) and if the grade lowers during follow-up (example Grade 1), it would be entered as a Grade 1 Post Treatment Adverse Event, along with the Grade 2 Adverse Event.

2.3.3.2 Collection of toxicities at each follow up visit may be done by phone. Also, update ALL stop dates for applicable toxicities that are no longer occurring at follow up. ****NOTE:** See section 3.3.4 for guidance on Stop Dates for toxicities if the patient expires.

2.3.4 See each treatment study protocol for Adverse Event reporting guidance.

****NOTE**: Please group toxicities/Adverse Events together prior to updating to ensure the toxicity isn't being over reported. PCG is not able to review all data prior to sending to the physician/requestor and we would like to ensure we do not over report and provide clean data.

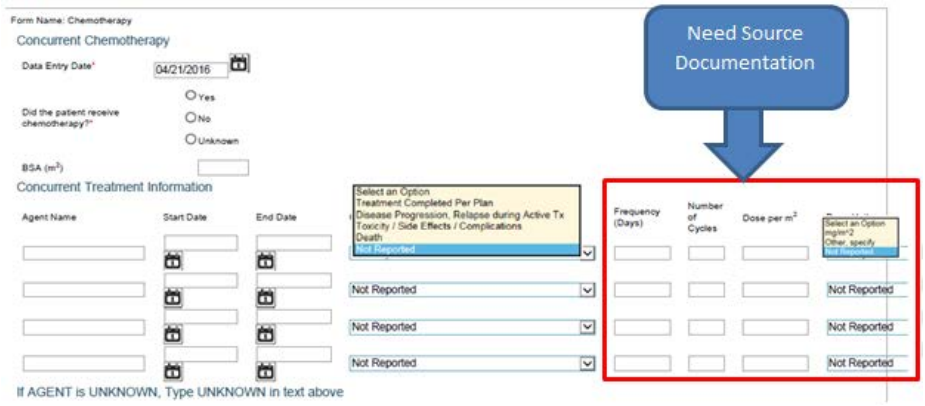
Data Entry Date	AE Type	Adverse Event	Click tab to group AE's		Stop Date	Form Status
08/02/2013	Baseline / Pre-Tx	Urinary urgency	1	10/01/2012	01/15/2013	Complete
02/06/2015	Adverse Event	Urinary urgency	2	07/17/2014	01/16/2015	Complete
02/06/2015	Adverse Event	Urinary urgency	1	01/16/2015	02/15/2016	Complete
08/12/2014	Adverse Event	Urinary urgency	2	07/17/2014	01/16/2015	Complete

2.4 End of Treatment/Summary Forms – If a patient decided not to move forward with radiation, this is a "Screen Failure" (see section 3.3.5) and eCRFs are not to be abstracted.

2.4.1 If a patient is receiving radiation at another site and you are able to gather the source documents, complete the eCRFs and do not mark patient as a "Screen Failure".

2.4.2 Chemotherapy- if chemotherapy started prior to radiation but continued throughout radiation, this is considered concurrent with radiation and would be included on this form (rather than the Prior Treatment form).

2.4.2.1 BSA— (Body Surface Area)—for clinical purposes BSA is a better indicator of metabolic mass than body weight because it is less affected by abnormal adipose mass.



2.4.3 Dosimetry (**only applicable for treatment studies**)- upload source document into the EDC Appendix (see section 4.0)

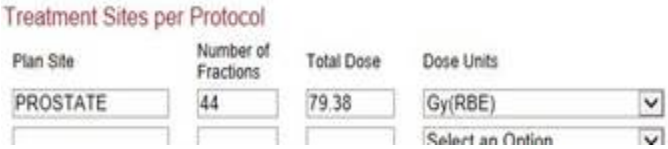
2.4.4 Meds at EOT (**only applicable for Prostate**)- medications started ***during*** radiation for urinary symptoms (including OTC medications)

2.4.5 Radiation Treatment

2.4.5.1 Treatment Summary

2.4.5.1.1 If the patient received **PROTONS**, the dose will be recorded in the medical record as CGE or Gy (RBE). In Velos, you would indicate Gy(RBE) from the drop down

menu:



2.4.5.1.2 If the patient received **PHOTONS**, the dose will be recorded in the medical record as Gy or cGy. In Velos, you would indicate Gy from the drop down menu:

****NOTE:** If the doses in the medical records are recorded for photon patients using cGy (or proton patients using cGy(RBE)), you will have to properly convert them to Gy (or Gy(RBE)) for Velos entry. This is done by dividing the cGy (or cGy(RBE)) dose by 100. For example, if the medical record indicates a photon dose of 5000 cGy, this will be entered into Velos as 50.00 Gy.

2.4.5.1.3 Treatment Frequency – how often treatment occurs (for example, daily, every other day)

2.4.5.1.4 Treatment Type – Other (specify in Comment) can be used if the patient received electrons or some other form of radiation.

2.4.5.1.5 Type of Proton Modality – Only applicable for proton radiation. For all other radiation, please use Not Applicable.

2.4.5.1.6 Motion Management Strategy – Only applicable for certain disease sites (for example, breast, lung). May be found in the Orders or Simulation Note.

2.4.5.2 Total Cumulative Dose (Proton Only)—combine the total dose for proton treatment only. If patient did not receive any protons, please enter "0".

2.4.5.3 Total Number of Treatment Fields - total number of treatment fields in the patient's treatment plan (regardless of treatment schedule)

2.4.5.4 Unscheduled Interruptions in Radiation

2.4.5.4.1 Facility closings such as for holidays are **NOT** considered unscheduled interruptions for REG001-09

2.4.5.4.2 For treatment trials, review each individual protocol as each has its own specifications for unscheduled interruptions

2.4.5.5 Reason Radiation Treatment Ended

2.4.5.5.1 If the original treatment plan was followed (prescribed dose received), indicate "Treatment Completed as Required".

2.4.5.5.2 If the patient does not complete the prescribed number of fractions (prescribed 44 fractions and only completed 39 fractions), indicate a reason why the treatment ended earlier than anticipated per plan.

2.5 Follow-up Forms – data entered since the last evaluation

2.5.1 Follow up schedules:

2.5.1.1 GU002-10 section 11.0 Patient Assessments

2.5.1.2 GU003-10 section 4.0 Patient Assessments

2.5.1.3 BRE007-12 section 4.0 Patient Assessments

2.5.1.4 BRE008-12 section 4.0 Patient Assessments

2.5.1.5 LUN005-12 section 4.0 Patient Assessments

2.5.1.6 REG001-09 section 5.2 Data Collection (**ANNUAL/YEARLY required starting April 2015**)

2.5.2 For death of any patient, please enter a separate Follow-up eCRF (with Patient Status of "Dead") along with updating the Status of the patient under Screening/Enrollment. For Status information, see section 3.3.4.

2.5.3 Date of Last Contact- this should be the most recent date information was received for REG001-09 only. For example, if the date of an office visit was on 9/1/2015 and an MRI was not completed until 9/15/2015, please enter the date of last contact as 9/15/2015 and the contact type can still be marked as office visit. The date of last contact does not apply to the follow up visit type, only the last date your site had contact with the patient for the follow up visit being entered. ****NOTE:** For treatment protocols, the date that is within the allowed visit window should be the date of last contact to avoid Deviations/Missed Visits being entered when the patient actually had a follow up completed within window. Please keep in mind that all mandatory visit assessments must be completed within the visit window.

2.5.4 Missed Visit (treatment protocols ONLY) should be entered as a follow up by **PCG Staff ONLY.** This visit is entered when PCG has received and reviewed a deviation from the site. This visit is also used when a follow up is out of the allowed window. Missed Visits should be deleted, if necessary, by **PCG Staff ONLY**.

2.5.4.1 If a patient was seen **WITHIN** the protocol defined visit window (example: target date +/- 45 days):

2.5.4.1.1 Enter the visit with the "Follow-up time point (months)" as the **target** month (example: seen in month 13, but within 45 days of the month 12 visit, enter as "12")

2.5.4.2 If the patient was seen **OUTSIDE** of the protocol defined visit window:

2.5.4.2.1 Enter the visit with the "Follow-up time point (months)" as the **actual** month (example: seen in month 28, rather than month 24 as per protocol, enter as "28")

2.5.4.2.2 Complete a PCG Protocol Deviation form, stating that patient was seen out of window for the month 24 visit

2.5.4.2.3 PCG will enter a "Missed Visit" for month 24 (this allows us to confirm a Protocol Deviation has been submitted)

2.5.5 Subjects may not return to sites for follow-up visits. Therefore, as much information as possible should be obtained from outside physicians, labs, etc. Assessments can be performed over the phone (and documented in the EMR). QoL forms can also be sent to subjects for completion.

****NOTE:** Please ensure all Baseline and End of Treatment eCRFs have been completed PRIOR to entering any follow-up information. Once these eCRFs are complete, the in Follow-Up Status can be added and Follow-up eCRFs can be entered.

2.6 Additional Forms – Disease Specific

2.6.1 Quality of Life Form- completed at designated visits per treatment studies (Prostate and Breast) and site's standard of care (REG001-09)
****NOTE:** forms are different for Prostate and Breast

2.6.2 Cosmesis Form (Breast Studies)- completed at designated visits by designated staff member per protocol

2.6.3 Acute/Late Skin Toxicity Form (Breast Studies)- completed at designated visits by designated staff member per Delegation Log

2.7 Form Status

2.7.1 FORM INCOMPLETE- used when data entered needs further review or source is not located in the medical record. This status should only be temporary and should not be the final status of the form. Queries will be issued if form status is used 30 days or longer.

2.7.1.1 Form Incomplete should **NOT** be used for ELIG and Adverse Events eCRFs. For ELIG, the patient should have signed the consent and the documentation of consent be completed PRIOR to registration/enrollment into the EDC. Adverse Events/Toxicities may last for months or years, so the first time a toxicity is noted the Form Status should be marked as Complete.

Calendar/Schedule (eCRF packet) in the EDC system when enrolled. If you have questions regarding how to classify a subject's Treatment Arm or Calendar/Schedule, please contact PCG at **HQ@pcgresearch.org**.

3.1 REG001-09 Calendar/Schedule Guidelines: See Appendix I

3.1.1 Incorrect Treatment Arm: May be updated by site. ****NOTE**: Only one treatment arm per patient ID.

3.1.2 Incorrect Calendar/Schedule: Please send an email to **HQ@pcgresearch.org** to make the appropriate correction.

3.1.3 Supplemental information:

3.1.3.1 Metastasis: per NCI definition, the process by which cancer cells spread to other parts of the body. For many types of cancers, it is also called Stage IV (four).

Cancer Type	Main sites of Metastasis (Per NCI Website)
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung, peritoneum
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, contralateral lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum
Pancreas	Liver, lung, peritoneum
Prostate	Adrenal gland, bone, liver, lung
Rectal	Liver, lung, peritoneum
Stomach	Liver, lung, peritoneum
Thyroid	Bone, liver, lung
Uterus	Bone, liver, lung, peritoneum, vagina

3.1.3.2 Invasion (local): tumor directly extends into adjacent tissue. For example, tumor of the floor of mouth which invades into the adjacent jawbone (mandible), the invasion will be next to the original tumor. See Appendix I for classification guidelines.

3.1.3.3 Spread to the lymph nodes is another form of metastasis but this is frequently considered "regional spread" and not distant metastasis. Physician discretion should be used if there is no clear documentation.

3.2.1.2 Additional information in regards to the Treatment Arm can be entered in the Notes section. For example, if Treatment Arm is "Metastatic Disease", notes can be added such as "prostate primary, treating bone metastasis". This is highly recommended but not mandatory, as this field helps PCG eliminate additional requests for data if completed.

3.3 Adding a Patient Status

3.3.1 **"Enrolled"** is the first status each subject is to be registered under. For randomized studies, this indicates randomization. ****NOTE:** Enrolled status should never be deleted. For example, if a patient is found to be a screen failure, there should be both an "Enrolled" (first status entered) and "Screen Failure "status. Dates should not be the same, see section 3.3.5 for further instructions.

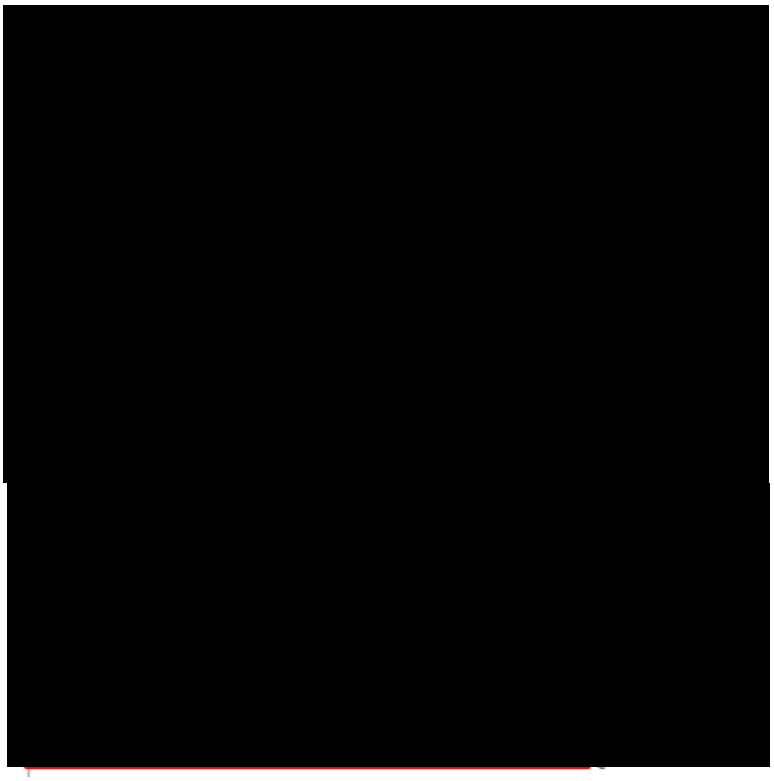
3.3.2 **"In Follow-Up"** is once the patient has completed radiation and ALL Baseline, Adverse Event and End of Treatment eCRFs have been abstracted. Once these are complete, the status "In-Follow Up" should be added. ****NOTE:** If patient "Enrolled" during follows up visits, there should be both an "Enrolled" (first status entered) and "In Follow-up" status. The "In Follow up" Status Date should be the day after the "Enrolled" status date. These dates should not be the same date.

3.3.3 **"Off Study"** is for patients who have withdrawn consent from the study.

3.3.3.1 Patient Withdrawal from Protocol Treatment (non-registry studies) – If the patient elects to withdraw from receiving protocol treatment, site staff should send written notification to PCG at **HQ@pcgresearch.org**. This documentation should also become a part of the subject's chart and be identifiable by the monitor. The site is still expected to collect as much follow-up data as possible (as consent to use information has not been withdrawn, see section 3.3.3.2). This data collection is important to assess long-term outcomes.

3.3.3.2 Patient Withdrawal from Study and Withdrawal of Consent – If the patient withdraws consent and withdraws from the study, site staff should send written notification to PCG at HQ@pcgresearch.org. This documentation should also become a part of the subject's chart and be identifiable by the monitor. Once the withdrawal of consent occurs, the site should not collect further data. Data collected prior to the withdrawal of consent can still be used by PCG and its member sites.

3.3.4 **"Off Study due to Death"** is for patients who have expired. Please complete the Patient Status section for death (bottom of form). ****Reminder**: Enter a follow-up visit with the Patient Status of Dead and add a STOP date to all on-going toxicities in the Adverse Event



3.3.5 **"Screen Failure"** is for patients who signed the consent form but did not proceed with radiation at your facility. This also indicates your site will not be receiving any further treatment information on the patient, if they are receiving radiation at an outside facility. The date of screen fail should be either the date deemed this status or the day after "Enrolled" (if date determined the same as the enrolled date). ****NOTE:** eCRFs do not need to be completed and PCG will remove calendar/eCRF packet.

3.3.5.1 Due to the REG001 amendment to include other forms of radiation, if a patient is deemed a screen fail, PCG requires additional notes regarding the reason for this status.

3.3.5.2 For treatment trials only, send email notification for all screen fails to **HQ@pcgresearch.org.** Sites are NOT required to send email notification for patients on the REG001-09 study due to the number of patients on this study.

3.3.6 **"Lost to F/U"** is for patients that several attempts have been made to schedule a visit but failed. See SPM for each protocol for details regarding required number of attempts and timeframe. ****NOTE:** For treatment protocols, these patients will continue to be on monthly compliance reports. The site is asked to review if the patient came back or outside documentation on survival status was received.

3.3.7 **"Follow-Up Off Protocol"** is for patients that are non-compliant with follow-up, have a deviation waver/planned deviation on file, or treatment study patients with disease progression.

3.3.7.1 In order to be used for REG001-09 patients, the following criteria must be met:

3.3.7.1.1 Patient is more than 1 year overdue for data entry AND

3.3.7.1.2 Site has made an effort to get info but is not able AND

3.3.7.1.3 Site thinks they will be able to get at least survival information in the future

3.3.7.2 Data, if available, is still collected on the patient. The goal is to still collect information that affects the primary endpoints (toxicity, disease status, mortality).

3.3.7.3 SAEs are still reported (if known).

3.3.7.4 Documentation needed explaining the reason patient given this status (in EMR or Velos – see Note below).

****NOTE:** There is an option to add additional Notes when updating the status. This field is not required but is *highly recommended* for Off Study due to Death and Follow-Up Off Protocol. This field may need to be completed upon PCG request. However, additional notes are required for Screen Failure and Lost to F/U status (documentation of attempts to contact patient).

****Dates cannot be the same date for each Status.** ****