Procedure for testing setup reproducibility for patients treated using stereotactic body radiation therapy (SBRT) methodologies combined with respiration control

1) Requirement BEFORE entering your first patient on a stereotactic body radiation therapy (SBRT) protocol - Perform a single-patient setup reproducibility and targeting study using one of the following methods: serial CT sessions with the patient repositioned between each procedure, repeat orthogonal planar images, or an equivalent study devised by you and discussed with and accepted by the ITC. The number of repeat imaging sessions must be at least four so that the total number is an initial imaging procedure plus four additional procedures. The studies can be mixed in that four planar orthogonal radiograph pairs can be compared to an initial planning CT study. In this case, the CT study can be used to generate DRRs that are matched to the geometry of the orthogonal radiographs. These DRRs are then used for comparison. The testing method selected must employ the same technique that will be used to control respiration during treatment. For example, if a compression paddle is used for the abdomen to suppress breathing motion, the CT or other imaging studies must be gathered with this equipment in place. The total number of patients studied will be five, but only one patient will be done off-protocol. Since this first patient will not be accepted for accrual to the protocol, it is not necessary to exactly meet all of the protocol requirements. However, the patient must be under treatment for a single lesion or multiple lesions in either the liver if credentialing is for RTOG protocol 0438 (originally 0245) and the lesion or lesions must be in the lung for RTOG protocol 0236. Also, the targets should not be grossly different in size relative to the specifications given in the protocol. (Note: If you do not have a large population of patients that meet the protocol requirements, your institution has the option of studying all five patients using the procedure described in this step that does not require exact protocol compliance. Submission for accrual to the protocol will be allowed at some point in the future after the results of this study have been analyzed.)

The results of any of the studies discussed in general above and detailed below will be sent to the ITC for review and acceptance. The institution is expected to perform the study, but quantitative information must be clearly indicated so that all measurements can be checked for accuracy. When the results for an initial patient have been accepted by the ITC, the institution can proceed with step #2 described below that does allow patient accrual to the protocol and is designed for those institutions that do have access to a significant number of patients that meet protocol requirements.

In the case of RTOG protocol 0438 (originally 0245), the study described here will be used to define the margins that will be set for all additional patients entered on the protocol. Thus, it is suggested that the margins used for this initial group of patients are set on the larger side of the mandated 0.4 to 10.0 mm range so that accrual can proceed if deviations exceed anticipated values. After this study is complete, margins can be adjusted based on the results obtained.

2) **Requirement for entering the first patient on the protocol** – In order to accelerate the process of starting accrual to the SBRT protocols, a procedure is described here for submitting

the 2nd to 5th patients of this study for accrual to the protocol. Step #2 and the ones that follow will add four patients to the study aimed at documenting setup reproducibility for your institution. Thus, these steps will add four additional patients that can potentially be accrued to the protocol. If an institution cannot demonstrate reproducibility that is consistent with the margins set in the protocol for any of the four additional patients intended for protocol accrual, the particular patients will be recorded as a major variation and will not be accepted for accrual.

A second patient must not be entered on the protocol until the results for the first patient entered are reviewed and accepted. A rapid review will not be attempted.

3) **Requirement for entering the second and third patients on the protocol** – If the results for the first patient intended for accrual to the study are acceptable, a second and a third patient can be entered on the protocol. These patients can be entered together in that acceptance of the results for one patient does not affect placing the other patient on the protocol. However, the results for at least two patients must meet the approval of the ITC before the final patient contributing to this positioning and targeting study can be entered on the protocol.

4) **Requirement for entering the fourth patient on the protocol** – Upon acceptance of the results for at least two patients entered on this reproducibility and targeting study, the fourth and final patient can be entered on the protocol.

5) Requirement for entering additional patients on the protocol – When the data submitted for the first four patients submitted for accrual to the protocol has been accepted by the ITC, institutions can enter patients without obtaining the additional imaging studies that are described here. However, each protocol has different requirements for obtaining periodic (usually weekly) check images, and these requirements must be met independent of the results of this study.

Procedures for gathering quantitative information from imaging studies:

The procedures described here will require Institutional Review Board (IRB) approval when patients receive an additional dose of radiation to obtain the images needed for this credentialing study. In some cases, it might be possible to retrospectively analyze existing image data to obtain the setup reproducibility information. Performing the study in this way will not result in extra radiation dose for the patient. Alternatively, when the immobilization and/or localization equipment is FDA approved and used routinely at your institution, it is possible to launch a prospective quality assurance review of standard weekly portal images to gather the information needed to complete this study. Using either a retrospective or prospective approach to analyze weekly portal images may require IRB approval, but the assumption is that this approval will be relatively easy to obtain in that no additional radiation is given to the patient. The obvious drawback to the prospective analysis of weekly portal images is that the data must be gathered over a long period of time. Obtaining planar images with an electronic portal imaging device (EPID) each day of treatment will not give added dose to the patient if two of the portals used for treatment provide the images. However, small fields will be used for most SBRT protocols and it is unlikely that any useful anatomic landmarks will be seen on the images. It is for this reason that it is recommended that a prospective study that uses daily imaging with over-flash double exposures be used for this credentialing.

Performing a CT study on different days will result in an extra dose for the patient. A study of this type will require an IRB application.

CT Procedure:

Measuring linear deviations along the inferior/superior, anterior/posterior and lateral directions within the patient is straightforward when CT transverse images are available. This task can be accomplished by employing measuring tools that exist on most modern CT units. The accuracy of such measurements depends on the image pixel size as well as the observer's ability to identify the target position, the location of target surrogates in the form of useful anatomic landmarks, and the reproducibility of the placement of radio-opaque markers that correspond to setup points on the patient skin surface. Any deformation of the patient from one imaging session to the next will add to the uncertainty of target localization. Along the patient's major axis, resolution is determined by the slice spacing of the CT images and will usually exceed the limits achievable within a transverse plane. Fusion of the various scans is the major tool to be used to demonstrate the ability of your institution to work with the margins required under the particular SBRT protocol you are considering. However, as described below, simpler procedures can also be applied when fusion software is not available. The purpose of the study described here is to determine the amount of daily variation of the target center and its surface relative to the skin marks used to set up the patient.

The CT procedure will usually employ radio-opaque markers or beebees placed at the position of the skin marks used for daily patient setup. The different follow-up image studies can be fused with the initial planning study so that the skin marks are brought into the best possible agreement. This fusion step simulates the normal setup reproducibility where the therapists position the patient to obtain laser light agreement with available skin marks. (If a stereotactic body frame is used for treatment, the procedure is modified to make fiducial markers contained within the body frame agree with the room laser lights. Of course, some body frame devices have their own laser system for positioning the patient in the box.) When fusion software is not available, measurements must be taken relative to some point that is referenced to skin markers. This point is usually the position of the isocenter for the treatment fields.

For liver CT studies, where the target may not be readily visible, the entire organ can be contoured as an indicator of targeting reproducibility. The difference in the position of the center of mass of the contoured liver is used to quantify the amount of daily setup variation. The same procedure can be used for lung lesions, but in this case it is advisable to try to contour the individual lesions instead of the entire lung.

As an alternative to taking measurements from CT scans, orthogonal planar images can be used. This procedure requires visualization of the lesion when respiration is not completely controlled (e.g., shallow breathing), or the use of surrounding anatomy surrogates when breathing is completely suspended. The procedure for extracting setup deviations from a set of orthogonal planar images is given below for the situation where various anatomical surrogates are used as a reference for the measurements.

Orthogonal Planar Imaging Procedure:

The methodology used for this study is taken from an article published in 1992 (1). The method was applied at that time to the situation where imaging data is in the form of orthogonal radiographs that are in the Anterior to Posterior or P to A direction plus the right or left lateral direction. The same method can easily be used for orthogonal EPID images that are not in agreement with the AP or lateral axis of the patient.

The procedure for collecting data requires the gathering of a series of linear measurements to demonstrate the accuracy of placement of the treatment fields for the equipment you intend to use for patient immobilization and/or localization when accruing for this protocol. The paragraphs that follow give the procedure for extracting data from an orthogonal pair of images.

The procedure depends on the identification of anatomic landmarks that can be used as a reference for field placement. The shift of these landmarks within the treatment apertures will be used as a measure of the shift of the treatment unit isocenter relative to the patient's bony anatomy. These landmarks should be, as much as possible, small points in the patient's body. However, it may not always be possible to identify such small anatomic points. Thus, some compromise may be necessary. Structures like the femoral heads can be used when the center of this fairly spherical structure can be used as a point in space. Remember that it is often the case that some point might be easily identified in one orthogonal view, but not other orthogonal direction. This situation is not helpful in terms of obtaining the information needed to perform the study described here. The same point must be recognizable in both orthogonal views.

The procedure described here will determine both the systematic and random fluctuations for the system you use for immobilization and localization. If your patient setup procedure includes

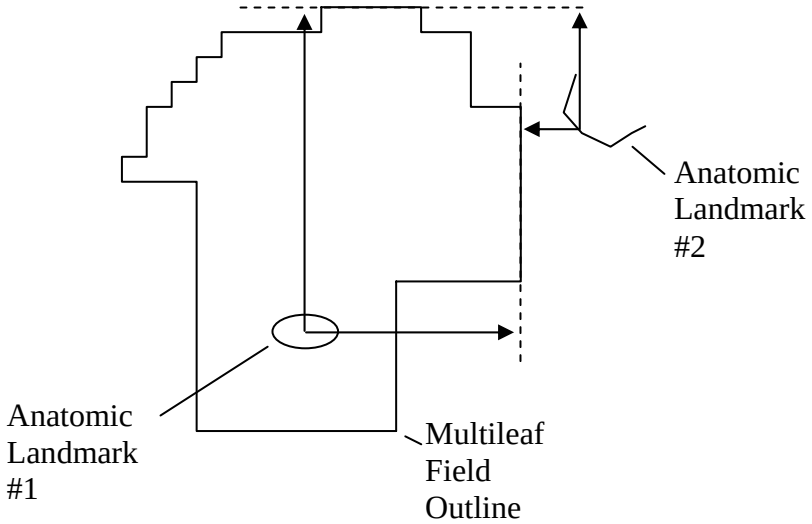

Figure 1

adjusting the patient's position for an initial port filming session, this should be noted in the questionnaire that is attached to this document. Any changes in the patient's setup information during the course of treatment should also be noted on the questionnaire.

When a double exposure that includes the beam outline is available, the details of the field aperture edge can be used as a reference for the measurements taken from each orthogonal view. Alternatives like identifying the image matrix center can be used when double exposures are not obtainable. Using the field edge as a reference is relatively easy when a multileaf collimator is used for aperture definition (see **Figure 1**). In this case the leaf steps can be used to accurately identify fixed locations around the edge of the apertures. For each film and each anatomic landmark, two measurements are taken. As shown in the figure, one measurement is to determine if the field is shifted in either the superior or inferior direction (see the arrows pointing up in the figure). The second measurement indicates any side-to-side shift of the field (see the one arrow pointing left and the other arrow pointing to the right). When viewing the field outline using an EPID, it is important to adjust the window and level for the display so that the size of the beam elements around the edge of the field are not distorted.

In order to use the field outline as a reference, this procedure must start by checking to be sure that the field shape and collimator rotation is correct. After extracting the linear measurements for the first film, the same anatomic landmarks are identified in the second film and the procedure is repeated for this orthogonal view. Although it is helpful in understanding Figure 1 and the equations that follow to visualize the orthogonal image pair as having their center axes lying in a transverse plane through the patient, this is not a strict requirement and other orientations that do not have either of the orthogonal views aligned with a transverse plane are possible.

In order to determine the random fluctuation of the isocenter location, measurements taken each day are compared to the average position of the isocenter for all treatments. The equation (1) can be used to calculate the mean deviation from the average value taken over all days used for imaging. Systematic errors associated with the move from simulation to treatment are determined by comparing the isocenter position at the time of sim to the average position for all of the treatment data points. Using the simulation CT information, it is possible to generate Digitally Reconstructed Radiographs (DRRs) that correspond to the two orthogonal images referred to above. Thus, the goal of this study is to determine the mean deviation of the isocenter position averaged over the number of landmarks selected. The mean deviation is a linear shift in mm for all measurements taken relative to the isocenter position at the time of simulation. The equation for determining the random day-to-day deviation can be written as follows.

$$(R.E.)_j = \left[\frac{\sum_{k=1}^{n} \left(x_{jk} - \bar{x}_j\right)^2 + \sum_{k=1}^{n} \left(y_{jk} - \bar{y}_j\right)^2}{n} \right]^{1/2} \quad \text{where } \bar{x}_j = \frac{\sum_{k=1}^{n} x_{jk}}{n} \text{ and } \bar{y}_j = \frac{\sum_{k=1}^{n} y_{jk}}{n} \qquad (1)$$

The quantities $\bar{x}_j$ and $\bar{y}_j$ are the average *x* and *y* shifts for the *j*th landmark. The index *k* refers to the *k*th day of imaging. This equation compares the daily deviation to the average value. Any systematic error introduced in the process of going from simulation to treatment is determined by applying the equation

$$(S.E.)_j = \left[(\bar{x}_j - x_{j0})^2 + (\bar{y}_j - y_{j0})^2 \right]^{1/2} \quad (2)$$

where the "0" indicates the value taken from simulation. In order to find the overall mean random or mean systematic error, it is necessary to average the results over the number of landmarks used. Thus, the following equations can be used to obtain the final results to be reported here

$$averageR.E. = \sum_{j=1}^{j_{max}} (R.E.)_j \qquad averageS.E. = \sum_{j=1}^{j_{max}} (S.E.)_j \quad (3)$$

All data must be submitted digitally. Film can only be used if they are scanned and the images are transferred digitally. All measurements must be annotated on the images so that they can be checked by the PIs for this protocol.

REFERENCES:

Rosenthal, S.A., Galvin, J.M., Goldwein, J.W., Smith, A.R., Blitzer, P.H.: Improved Methods for Determination of Variability in Patient Positioning for Radiation Therapy Using Simulation and Serial Portal Film Measurements. *Int. J. Rad. Oncol. Biol. Phys.* **23**:621-625, 1992

Data Page

Patient Name:_____

Simulation Information

Landmark Code	Landmark Name	Date: x_1	y_1
A			
B			
C			

Daily Portal Imaging

Landmark Code	Landmark Name	Fraction #	Date: x_1	y_1	Date: x_2	y_2	Date: x_3	y_3	Date: x_k	y_k
A										
B										
C										