

**Evaluation of novel cone-beam CT for guidance and adaptation of  
precision radiotherapy**

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24 January 2022**

**Sponsor:**

**Varian Medical Systems  
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Palo Alto, CA 94304 USA**

## Evaluation of novel cone-beam CT for guidance and adaptation of precision radiotherapy

Summary of Changes from Previous Version:

Version	Affected Section(s)	Summary of Revisions Made	Rationale
1.0		Initial Release	
2.0	Protocol signature page	Corrected version date	Administrative
	Synopsis	Fixed typographical error	

## Abbreviations

AE	Adverse event
API	Application programming interface
CBCT	Cone beam CT
CIP	Clinical investigation plan
CNR	Contrast-to-noise ratio
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DEBH	Deep expiration breath hold
DIBH	Deep inspiration breath hold
EC	Ethical Committee
HR	Human resources
HU	Hounsfield Unit
IGRT	Image-guided radiation therapy
IRB	Institutional Review Board
ISO	International Organization for Standardization
NS	Nova Scotia
NSHA	Nova Scotia Health Authority
QE2	Queen Elizabeth II
REB	Research ethics board
RT	Radiation therapy
SABR	Stereotactic Ablative Radiation Therapy
SAE	Serious adverse event

## **Evaluation of novel cone-beam CT for guidance and adaptation of precision radiotherapy**

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### **Protocol Signature Page**

I have read and understood this clinical investigational plan and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will ensure they are fully informed regarding the investigational device and the conduct of the study according to Good Clinical Practices, applicable federal, state and local regulations, and Institutional Review Board (IRB) / Ethical Committee (EC) requirements. I agree to collect and report all study data according to this clinical investigational plan.

Investigational Site Name:	Site Abbreviation:
Principal Investigator (print name):	Location:
Principal Investigator (signature):	Date:

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## SYNOPSIS

<b>Title:</b>	Evaluation of novel cone-beam CT for guidance and adaptation of precision radiotherapy
<b>Study Description:</b>	This is a feasibility study investigating the image quality of a new, high-performance cone beam CT (CBCT) used for on-couch imaging during radiotherapy treatments.
<b>Objectives:</b>	<p><i>Primary Objective:</i> Compare – quantitatively and qualitatively – CBCT images acquired by the high-performance system to both CBCT images acquired using a standard system and to fan beam CT images acquired for radiotherapy dosimetry planning.</p> <p><i>Secondary Objectives:</i> (1) Compare the radiation dosimetry calculated from the high-performance CBCT images to that calculated from both standard CBCT images and fan beam CT images. (2) Compare the patient experience between faster acquisition of the high-performance CBCT, which enables acquisition with a single breath hold, versus slower acquisition of a standard CBCT requiring potentially multiple breath holds.</p>
<b>Metrics:</b>	<p>Images will be evaluated quantitatively by calculating contrast-to-noise ratio (CNR), resolution, Hounsfield Unit (HU) accuracy and artifact reduction.</p> <p>Radiation oncologists and radiation therapists will compare image sets and rank them according to usefulness for anatomical structure delineation and patient positioning, respectively.</p> <p>Anatomical structures from a subject's dosimetry plan will be deformably registered from the planning fan beam CT to the CBCTs acquired for that subject. Dosimetry will be calculated from all three registered image sets and dose-volume histograms will be compared.</p> <p>Subjects will complete a questionnaire evaluating their experience of the two different CBCT acquisition processes.</p>
<b>Study Population:</b>	Adult cancer patients undergoing radiotherapy where a breath hold is required for imaging and/or treatment delivery.
<b>Phase:</b>	Feasibility study

<b>Description of Sites/Facilities Enrolling Participants:</b>	This is a single-site study that will take place at the QE2 location of Nova Scotia Health.
<b>Description of Study Intervention:</b>	Two additional CBCT images will be acquired, one with a breath hold, the other with free breathing. Participation in the protocol will not alter a patient's cancer treatment.
<b>Study Duration:</b>	One year
<b>Participant Duration:</b>	1-4 weeks

# 1 INTRODUCTION

## 1.1 Study Background and Rationale

This study focuses on potential benefits of a high-performance cone beam CT (CBCT) image guidance system for improved precision in the delivery of radiotherapy. This imaging system is a component of a forthcoming radiation therapy (RT) treatment platform, called Ethos (Varian Medical Systems), to be installed and commissioned clinically at the Nova Scotia Health QE2 site in Q1 2022.

Radiation therapy is used in the treatment of approximately 50-60% of all cancer patients. Image guided radiation therapy (IGRT) is now a standard of care for external beam radiotherapy. During an IGRT treatment session, a CBCT imaging system built into the treatment unit allows 3D visualization of the patient's anatomy immediately prior to, and, if required, at several time points during the delivery of radiation. The CBCT image data are used by the treatment team to carefully align the patient to their previously acquired treatment planning CT. Verification of the patient position and alignment with the treatment planning images increases the precision of radiation delivery. IGRT is available on all eight treatment units in Nova Scotia and is central to their procedures for delivery of precision RT.

Although IGRT has facilitated breakthroughs in the precision and accuracy of RT over the past two decades, the imaging technology has remained limited in some respects, particularly in the amount of time it takes to acquire a CBCT image. The current acquisition duration of approximately one minute does not allow image guidance in scenarios where high temporal resolution is required. This limitation is most evident in clinical situations where tumours move during treatment delivery, e.g., breast, liver, or lung tumours that move with the patient's respiration. In this scenario, both the CBCT image acquisition and radiation delivery is accomplished at NS Health by the patient performing multiple breath-hold maneuvers in an effort to 'freeze' the motion of the tumour, which may otherwise move by up to 3 cm. Deep Inspiration Breath Hold (DIBH) or Deep Expiration Breath Hold (DEBH) approaches are both used at NS Health, depending on the indication. Because complete acquisition of a CBCT image may require 60 seconds and because many patients who are treated with IGRT have limited ability to maintain DIBH or DEBH for extended periods, up to eight (Boda-Heggemann et al., 2011) separate breath hold maneuvers may be needed to acquire a complete image set.

The multiple-breath-hold CBCT acquisition approach has two key disadvantages. First, the total treatment time is significantly extended, especially if multiple CBCT acquisitions are required (e.g., for pre- and post-alignment of the patient, and particularly for patients with compromised respiratory function, who need time to recover from each breath hold). Longer treatment times impact resources (capital and HR) and are deleterious to the overall patient experience. Second, since each breath hold is not performed identically by the patient (e.g., in terms of breath hold amplitude),

inconsistencies are introduced in the reconstructed image data, resulting in poorer image quality. By forming an image from piecewise sets of projections, one per breath hold, image quality is compromised by motion artifacts (Kashani et al., 2006) due to the variability of the patient's anatomy between projection sets. An example of this from practice, in the context of Stereotactic Ablative Radiation Therapy (SABR) of the liver, is shown in [Figure 1](#).



Figure 1 Status-quo CBCT image used for guidance of Stereotactic Ablative Radiation Therapy (SABR) of the liver. Multiple breath-hold maneuvers necessitated by the acquisition of this dataset causes marked artifacts (white arrows) at the dome of the liver and compromises the accuracy of aligning the anatomy for treatment.

NS Health has been performing breath-hold CBCT guidance for many years for patients with primary or metastatic liver cancer, T1-T2 lung cancer, and left-sided breast cancer and thus the treatment teams are acutely aware of the limitations of the technique.

There exists a compelling need for rapid CBCT image acquisition for guidance of RT. To date, CBCT acquisition within the timeframe of a single breath-hold has been limited to pre-clinical investigations (Arns et al., 2019). The high-performance CBCT system being developed for the Ethos treatment platform will allow image acquisition within approximately six seconds and with increased x-ray efficiency. Most patients can maintain a breath hold for six seconds and so the high performance CBCT system can potentially acquire an image with a single breath hold in a clinical setting. This improvement should result in higher quality intra-treatment imaging and a better patient experience. The x-ray efficiency improvement has the potential to improve image quality or reduce imaging dose to the patient. Improvements in motion artifact suppression algorithms used in the image reconstruction process may even improve quality of images acquired during free breathing, i.e., without a breath hold, which would have a

positive impact for patients who cannot maintain a breath hold due to significantly compromised respiratory function.

As explained in the objectives below, we expect that the Ethos CBCT will introduce previously unrealized image quality and anatomy visualization for on-couch imaging that will improve the precision of treatment delivery. Should this be the case, the improvement in intra treatment image quality will influence clinical practice on multiple fronts. The potential improvements in precision that come from better on-couch imaging may enable hypofractionation of patient treatment, e.g., compression of a 20+ daily fraction treatment course to 5 fractions, because higher fractional doses can be delivered safely. Improvements in visualization of anatomy resulting from increased image quality may enable accurate online adaptation of a patient's treatment plan in the presence of inter-fraction anatomical change. It may also facilitate development of rapid treatment paradigms without the need for a simulation procedure. For example, a patient with spinal cord compression could both have a treatment plan generated from the Ethos CBCT and then receive treatment on the Ethos platform, reducing time to treatment to one hour instead of one day.

With minimal disruption for participating patients, this study will enable a comparison of (i) the patient's treatment planning fan-beam CT and (ii) the patient's status-quo CBCT on an existing treatment unit with (iii) the high-performance CBCT on Ethos. Image quality of the high performance CBCT will thereby be compared to both a best-case standard (fan-beam) and the status-quo for IGRT to isolate and identify improvements. Image quality will be quantified in terms of contrast-to-noise ratio (CNR), resolution, Hounsfield Unit (HU) accuracy and artifact reduction with a focus on anatomy germane to the image guidance task. A qualitative assessment of the different image datasets will also be performed through feedback from multiple observers (radiation oncologists and radiation therapists). Radiation doses to key treatment targets and organs at risk will be calculated from the high performance CBCTs to determine the suitability of the CBCT images for RT dosimetric planning. Patient experience will be evaluated through questionnaires.

Image sets (i) and (ii) are already acquired as part of standard-of-care for radiation treatment. Two additional CBCTs, one with breath hold and the other with free breathing, will be acquired from each subject on the Ethos platform for this study. Radiation treatment planning and delivery will not be altered due to patients' participation in this study. Patients will receive radiotherapy according to current departmental procedures and on the department's existing linear accelerator platforms.

## 1.2 Risk/Benefit Assessment

### Potential risks of this study:

In routine clinical practice, the standard IGRT workflow may involve multiple CBCT acquisitions during each treatment session to ensure proper patient alignment. Patients

enrolled in this study will undergo two additional research CBCTs (high performance CBCTs on Ethos), both of which will be acquired during a single treatment visit. The radiation dose associated with these two additional CBCTs is approximately 1/5000 to 1/1000 of the dose that the patient will be receiving from the radiation therapy itself. To put this additional dose into perspective, it is helpful to understand that in routine radiotherapy there is inherent and acknowledged uncertainty in the delivered radiation dose. This uncertainty can be 3-5% of the prescribed dose. The dose from the two research CBCTs represents just an additional 1/50th of the already existing uncertainty. Thus, for this patient group, there should be no statistically detectable harm from the two additional CBCTs, e.g., with regard to late effects of the additional radiation.

There is also a potential risk for loss of patient privacy associated with the collection of patient data for this study. This risk will be mitigated by collecting only data that are necessary for the analyses specified in this protocol, by linking data to an anonymized research identifier and by storing data in a secure location to which access is controlled and audited.

#### Potential benefits:

This study is being performed to assess the potential advantages of a high-performance CBCT image guidance technology for future patients who will eventually be treated using this platform. The results may influence the development of new workflows that improve precision of RT through image guidance, as well as workflows for dosimetric plan adaptation based on daily CBCT imaging. One of the key potential benefits for future patients resulting from these new workflows may be lower doses to healthy tissues and reduced toxicity from the radiation treatments. The new knowledge acquired in this study will facilitate implementation of Ethos at NS Health (multiple Ethos platforms are anticipated in a new facility slated to open in 2026). The results will also be of great value to the broader radiation oncology community.

There are no direct benefits expected to the subjects participating in the study. The high performance CBCT images acquired for this study will not be used to make clinical decisions. However, due to the anticipated improved image quality of the Ethos-acquired CBCT, the Principal Investigator may make observations that could improve image guidance for the patient on the actual treatment unit. Such observations will be communicated to the patient's treatment team and must be confirmed with standard imaging prior to making any potential changes in the patient's treatment.

#### Assessment of potential risks and benefits:

On balance, given that the dosimetric risks to patients are very low, and there is significant potential benefit to future patients, the benefits of the study outweigh the risks.

## 2 OBJECTIVES AND ENDPOINTS

### 2.1 Study Objectives

The **primary objective** of the study is to compare

- The quality of high-performance Ethos CBCT images (acquired with breath hold and under free breathing) with that of fan-beam CT (CT simulation) acquired with breath hold, where the latter represents a best-case benchmark; and
- The quality of high performance Ethos CBCT images (acquired with breath hold and under free breathing) with that of Truebeam CBCT acquired with breath hold, where the latter represents the status-quo for image guidance.

The **secondary objectives** of the study are:

1. To compare treatment dosimetry calculated on the Ethos CBCT images to that calculated on both the fan-beam CT and the Truebeam CBCT.
2. To compare the patient experience of CBCT image acquisition between the Ethos CBCT and the existing Truebeam CBCT.

### 2.2 Study Endpoints/Metrics

#### 2.2.1 Primary Objective Metrics

The quality of fan-beam CT, Truebeam CBCT, and Ethos CBCTs will be compared quantitatively using the following calculated metrics:

- Contrast-to-noise ratio (CNR)
- Resolution
- Hounsfield Unit (HU) accuracy
- Artifact reduction

Furthermore, the three image sets will be evaluated qualitatively by multiple observers with training in radiation oncology and image-guided radiation therapy, who will rank the images acquired for each subject by perceived quality/usefulness for structure contouring and RT guidance.

#### 2.2.2 Secondary Objective Metrics

Dose-volume histograms for key target structures and organs at risk will be calculated from the Ethos and TrueBeam CBCT images and compared to those from the existing dosimetric plan for each patient to determine the accuracy of the dosimetric calculations based on the CBCTs.

The patient experience with CBCT image acquisition will be determined through the use of a questionnaire comparing the TrueBeam CBCT image acquisition process to that of the Ethos CBCT process.

## 3 STUDY DESIGN

### 3.1 Overall Design

This is a single-site feasibility study designed to generate data describing the quality and applicability of on-couch high-performance CBCT imaging technology during external beam radiation therapy.

Subjects who are enrolled in this study will undergo two cone-beam CT image acquisitions in addition to their standard of care. A subject's participation in the study is considered complete once the study CBCTs have been acquired and the questionnaire about the subject's experience of CBCT image acquisition has been completed.

## 4 ELIGIBILITY

### 4.1 Inclusion Criteria

The study will be open to any patient who meets *all of* the following inclusion criteria:

1. Patient age  $\geq 19$
2. Patient is scheduled for treatment on one of the five TrueBeam platforms at the NS Health QE2 site.
3. Patient is receiving radiation therapy using a breath-hold technique (for example, lung, liver and left breast cancers).

### 4.2 Exclusion Criteria

A patient is excluded from the study if they meet *any of* the following criteria:

1. Patient is pregnant or has plans for pregnancy during the period of treatment.
2. Patient is unwilling to consent to participating to the study, or for whom informed consent is not possible.

## 5 Research Plan

### 5.1 Study Methodology

1. The methodology for treatment setup, CT simulation, treatment planning, image guidance and treatment delivery will be determined by the patient's treatment team and is not specified in this protocol. Enrollment in the study may occur after treatment delivery has started but must be prior to the fifth fraction.
2. Following completion of informed consent to participate in this study, the Ethos imaging will be scheduled immediately before or after one of the subject's first five scheduled treatment fractions. While there will be some flexibility in scheduling the session on Ethos, it will be advantageous for the study imaging to be performed as soon as possible after the CT simulation to minimize the potential for anatomical change over time. Two research CBCT images will be acquired, one with breath hold, the other with free breathing.

The Ethos unit will be installed in the same department as the patient's treatment unit therefore the acquisition of the additional study imaging will not require a separate visit. We anticipate the study imaging will require no longer than 15 minutes. No treatment delivery will take place on the Ethos unit during this study.

3. The patient's CT simulation data, TrueBeam CBCT image data and Ethos CBCT data will be exported from the treatment planning system(s) for comparative analysis of image quality as detailed below. The TrueBeam CBCT used in the analysis will be exported from the treatment session delivered on the same day that the Ethos CBCTs are acquired. Data will be anonymized during the export process. Exported image data will be stored in a password-protected folder on the network drive behind hospital firewalls.

### 5.2 Analysis of data

1. Image quality will be quantified by calculating contrast-to-noise ratio (CNR), spatial resolution, Hounsfield Unit accuracy, and presence/absence of artifacts in each of the four image datasets acquired for each subject. This will be done using analysis scripts developed in MATLAB and the Eclipse API (ESAPI, Varian Medical Systems) in the Nova Scotia Health Department of Medical Physics.

CNR will be quantified using

$$\text{CNR} = (|\langle P_{\text{ROI}} \rangle - \langle P_{\text{BG}} \rangle|) / (S_{\text{ROI}}^2 + S_{\text{BG}}^2)^{0.5}$$

where  $\langle P_{\text{ROI}} \rangle$  and  $\langle P_{\text{BG}} \rangle$  are the mean Hounsfield Units (HU) in a selected region of interest and proximal background region, respectively, while  $S_{\text{ROI}}$  and  $S_{\text{BG}}$  are the standard deviations of the HU values in the corresponding regions.

Spatial resolution will be assessed by comparing HU profiles of high-contrast detail in image sets. Artifacts will be assessed qualitatively.

2. The patient's treatment plan, which is originally calculated on the fan-beam CT dataset (as per standard protocol) will be recalculated on both the TrueBeam CBCT and Ethos CBCT datasets using the following process: Target volumes and organ-at-risk contours that are relevant to the anatomy being imaged will be transferred from the original treatment plan onto the CBCTs through an elastic deformation. The accuracy of the contour registration will be verified by a radiation oncologist and contours will be adjusted manually, if necessary, to ensure proper alignment with the underlying image prior to re-calculation of the dose distribution. The dose volume histograms from the original treatment plan will be compared to those generated from the three CBCT-based plans in terms of standard dosimetry metrics, i.e., target volume coverage and organ-at-risk sparing.
3. Anonymized fan-beam CT images, status-quo CBCT image and Ethos CBCT image data sets (with breath hold and with free breathing) will be presented to multiple observers for qualitative assessment of perceived image quality. Observers will include up to five radiation oncologists and five radiation therapists, who will answer questions on image quality for contouring and image guidance purposes, respectively. Image quality will be scored either as a simple ranking (1 to 3) or using a five-point Likert scale. This review will be done using the MeVis framework (see example, Figure 2) that allows centralized user management and authentication, ensuring controlled access to data with unique login credentials for each individual. In the case of Likert scale ranking, analysis will be performed using a Mann-Whitney test.

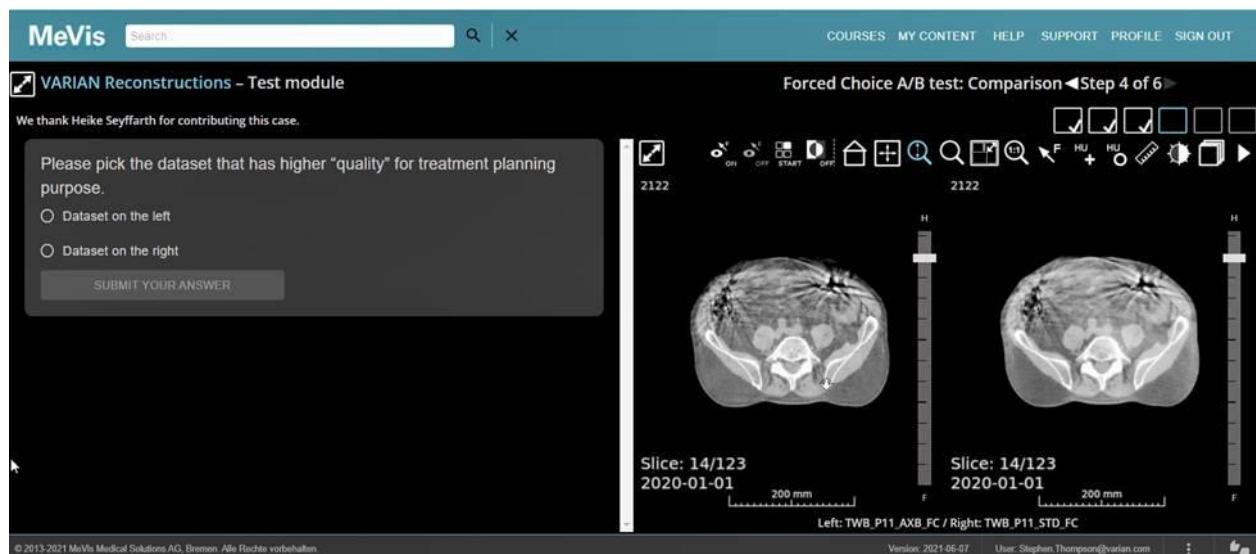


Figure 2 Example of qualitative image review using the MeVis framework.

4. A patient experience questionnaire will be provided to each subject on the day they undergo CBCT imaging on the Ethos platform. Subjects will be encouraged to fill out the questionnaire on that day. Study coordinators will transcribe subject responses into the study database.

### 5.3 Informed consent

All participating patients will be required to give written informed consent, indicated by a dated signature of the subject or legal representative. The process for obtaining informed consent shall comply with the ISO 14155:2020 and applicable national regulations and shall use language that is understandable by the patient. The original signed consent form shall be retained on file and a copy shall be given to the patient.

## 6 ADVERSE EVENTS

### 6.1 Expected Adverse Events

There are no adverse events expected from participation in this study. However, any adverse events attributed to participation in the study (“definitely”, “probably”, or “possibly” related) by the Principal Investigator will be documented and entered in the study database. Adverse events will be classified per CTCAE version 5.0. No other adverse events, including those that are attributed to the subject’s cancer treatment, will be recorded in the study database.

### 6.2 Adverse Event Definitions

Adverse events are “any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.”

A Serious Adverse Event (SAE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users, or other persons, whether or not related to the investigational medical device\* that:

- Led to a death,
- Led to serious deterioration in the health of the participant, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization\*\*, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

**\*NOTES:**

- NOTE 1 This definition includes events related to the investigational medical device or the comparator.
- NOTE 2 This definition includes events related to the procedures involved.
- NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

**\*\*NOTE** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Hospitalization means admitted to hospital for at least 24 hours. An emergency room, urgent care, or infusion center visit is not a hospitalization.

## **6.3 Adverse Event Reporting**

Study staff are required to notify the Principal Investigator of any serious adverse event (SAE). SAEs must be reported to the REB according to REB reporting requirements. The Principal Investigator must report SAEs to the study sponsor within 72 hours of becoming aware of the event.

Sponsor contact for AE reporting:

Sean Davidson  
Phone: (437) 991-8294  
Email: sean.davidson@varian.com

## **7 DEVICE ISSUES**

Any problems with the Ethos platform (including any device failures or malfunctions) will be documented and reported to the sponsor.

Per ISO 14155:2020, the following definition applies:

- Device Deficiency: inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance  
NOTE Device deficiencies include malfunctions, use errors, and inadequate labeling.

## **8 PROTOCOL DEVIATIONS**

Protocol deviations and other problems with study execution will be documented and reported to the sponsor and to the REB per REB reporting requirements.

## 9 DATA COLLECTION

### 9.1 Confidentiality Procedures

Only data that are required for the endpoints of the study will be collected. Study data include basic demographic information (age, sex), the location of the patient's tumor, co-morbidities that would affect breathing, and information about the image acquisitions. No data that can directly identify the subjects will be entered into the study database. Subjects will be represented in the study database by unique study identifiers. The relationship between patients and their study identifiers will be maintained in a protected master list located in a protected folder within the NSHA firewall (separate from the study database) to which only NS Health study personnel will have access.

All data that could directly identify the subject will be removed from the images collected for this study when they are exported from the clinical systems on which they are acquired.

### 9.2 Data Management

Data that are collected for this study will be kept in an electronic database hosted in a secure data center. Access to the de-identified study data will be limited to study personnel at NS Health and to the sponsor. Access to the data will be role-based, with specific permissions assigned to each role. Access to the study data will be through login credentials that are specific to the individual and access will be tracked via audit logs. Study data will be encrypted at rest. Access to the study database is via a secure web portal and data are encrypted in transit.

Paper documents such as completed subject questionnaires will be stored at NS Health in a secure location to which only study personnel have access.

The image data collected for the study – the treatment planning fan-beam CT, the TrueBeam CBCT and the Ethos CBCT – will be exported from the clinical systems on which they were acquired and stored in a secure folder behind NSHA firewalls accessible only to the study investigators and co-investigators. Images will be de-identified on export. The de-identified image data collected in this study will be shared with the study sponsor, Varian Medical Systems. De-identified image data will be transferred to secure data storage hosted by Varian via secure web upload. Access to the image storage will be limited to study personnel at NSHA and personnel at Varian. As with the study database, access to the image storage is by login credentials (username and a password) that are unique to the individual.

De-identified images will be uploaded to the MeVis system for qualitative evaluation. These images will be deleted from the MeVis system when the study is complete.

## 10 STATISTICAL CONSIDERATIONS

### 10.1 Sample Size

The study design does not involve any intervention in the subject's cancer care. The study is being performed to assess the image quality in a new CBCT system.

This study will accrue thirty (30) subjects, which will include:

- A minimum of 7 subjects with liver cancer
- A minimum of 7 subjects with lung cancer
- A minimum of 7 subjects with cancer in the left breast

Subjects with other cancers can be included so long as the patients meet the study's inclusion/exclusion criteria.

Seven subjects in each cohort will provide sufficient image data for a range of subject variation in the same anatomical site.

Data will be collected and analyzed as described in Section 5. Quantitative image quality metrics for the different imaging modalities will be compared using average values and standard deviations. Qualitative evaluations of image quality using a Likert scale will be compared using a Mann-Whitney test. Dosimetry will be compared using average values of metrics derived from dose-volume histograms and standard deviations of those values. Patient experience of the different CBCT acquisitions will be compared qualitatively based on responses to questionnaires.

## 11 REFERENCES

- Arns, A., Wertz, H., Boda-Heggemann, J., Schneider, F., Blessing, M., Abo-Madyan, Y., Steil, V., Wenz, F., & Fleckenstein, J. (2019). Ultrafast single breath-hold cone-beam CT lung cancer imaging with faster linac gantry rotation. *Radiotherapy and Oncology*, 135, 78–85. <https://doi.org/10.1016/j.radonc.2019.02.004>
- Boda-Heggemann, J., Fleckenstein, J., Lohr, F., Wertz, H., Nachit, M., Blessing, M., Stsepankou, D., Löb, I., Küpper, B., Kavanagh, A., Hansen, V. N., Brada, M., Wenz, F., & McNair, H. (2011). Multiple breath-hold CBCT for online image guided radiotherapy of lung tumors: Simulation with a dynamic phantom and first patient data. *Radiotherapy and Oncology*, 98(3), 309–316. <https://doi.org/10.1016/j.radonc.2011.01.019>
- Kashani, R., Koshani, R., Balter, J. M., Hayman, J. A., Henning, G. T., & Herk, M. van. (2006). Short-term and long-term reproducibility of lung tumor position using active breathing control (ABC). *International Journal of Radiation Oncology\*Biophysics*, 65(5), 1553–1559. <https://doi.org/10.1016/j.ijrobp.2006.04.027>