Evaluation of a Cone-beam CT scanner for Image Guided Radiotherapy (CONFIGURE)

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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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Principal Investigator: ***Dr. Ir. Wouter van Elmpt***		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

2D	**Two Dimensional**
ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
CBCT	**Cone-Beam Computed Tomography**
CNR	**Contrast-to-Noise Ratio**
CT	**Computed Tomography**
DVH	**Dose-Volume Histogram**
DSMB	**Data Safety Monitoring Board**
FOV	**Field Of View**
HU	**Hounsfield Units**
IB	**Investigator's Brochure**
IMDD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
RT	**Radiation Therapy**
(N)SCLC	**(Non-)Small Cell Lung Cancer**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: A novel cone-beam computerized tomography (CT) imaging system has been developed for image-guided radiotherapy. This new system can acquire cone-beam CT (CBCT) images faster than previous systems. Furthermore, the new system has demonstrated increased image quality, resolution and Hounsfield Unit (HU) accuracy in phantom images compared to previous cone-beam CT systems. This CBCT system opens new possibilities for use of CBCT images in various radiotherapy tasks for which previous CBCT images were not optimal. Specifically, the use of CBCT images for delineation of anatomical structures, radiotherapy treatment planning and radiation treatment dose calculation is limited with current on-board imaging technology. The improved image quality of the new system will be evaluated in a broad clinical setting and patient population with respect to its suitability for tumour and organ delineation, image-guided radiotherapy and radiation dosimetry for patients receiving external beam photon radiotherapy.

Objective: The main objective of this study is to evaluate the image quality of a new cone-beam CT imaging system that will be used to acquire images of a wide selection of anatomical locations in patients receiving radiotherapy for cancer.

Study design: Single arm, non-randomized prospective study.

Study population: Patients treated with external beam photon radiotherapy at Maastro. Six treatment/tumour sites will be investigated: head-and-neck, lung (stage I), lung (stage II-IV), left breast, pelvis, and (upper) abdomen. A total of 40 subjects distributed over the various anatomical sites will be enrolled with at least 5 subjects per treatment site.

Intervention: One additional imaging session with 1-2 additional CBCT image acquisitions will be performed using the novel cone-beam CT imaging device. The acquired images will not be used in any way to change the patient's treatment.

Main study parameters/endpoints: *Primary objective:* Qualitative comparison of the image quality of the novel cone-beam CT imaging system to standard cone-beam CT imaging and conventional fan beam CT imaging used for radiotherapy planning purposes.

Secondary objectives: Evaluation of the suitability of the novel CBCT images for radiation treatment planning and dose calculation. Qualitative assessments of novel CBCT vs. standard (cone-beam) CT images.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no direct benefit expected for the individual patients who participate in this study. Additional imaging is performed on the novel cone-beam CT imaging device using x-rays. Additional radiation exposure resulting from the two additional CBCT images acquired for this study is a small fraction (<0.1%) of the radiation received during a subject's standard radiotherapy treatment. Collected data will not be used for clinical decision making.

1. INTRODUCTION AND RATIONALE

Radiotherapy is administered to 40-50% of patients receiving treatment for cancer making it a standard treatment modality for a large number of patients. The radiation can be administered with high precision to the tumour while minimizing dose to the surrounding healthy tissue. Patient-specific radiation dosimetry plans are generated for patients receiving radiotherapy. A treatment planning fan-beam computed tomography (CT) scan is acquired using dedicated equipment (e.g., flat tabletop, laser-alignment based patient positioning, and dedicated CT scan protocols calibrated for radiotherapy purposes). Both the target (tumour) and the surrounding normal organs and tissues (so-called organs at risk) are delineated on the treatment planning CT, which forms the basis of an individualized treatment plan for each patient. Calibration of the treatment planning CT allows radiation doses to be calculated based on the CT Hounsfield numbers.

Radiation therapy is typically delivered in 25-35 daily treatments, or “fractions”, over the course of 5-7 weeks. Before every fraction of radiation treatment, images are acquired with the patient on the treatment table to ensure correct patient positioning and set-up (i.e., alignment with the patient position and set-up on the treatment planning CT). Daily images are acquired using imaging systems integrated with the treatment device (linear accelerator) [Jaffray 2012]. Typical on-board imaging systems produce either orthogonal 2D x-ray images or cone-beam CT (CBCT) images, the quality of which has historically been less than that of the treatment planning CT.

A novel cone-beam CT imaging system has recently been developed specifically for image-guided radiotherapy (Halcyon 4.0, developed by Varian, a Siemens Healthineers company). The new CBCT imaging system has the potential to optimize the image guidance workflow and increase the efficiency of the radiotherapy workflow. This new imaging system can acquire cone-beam CT images faster (i.e., by a factor of 3-6) than conventional CBCT systems and has a larger imaging panel resulting in an increased field-of-view (FOV). Image quality and Hounsfield Unit accuracy have increased compared to previous cone-beam CT image guided systems, as determined by evaluation of images acquired of phantoms. Furthermore, improvements have been made to the reconstruction algorithms used to convert the x-ray projections collected at multiple rotation angles around the patient into a 3D image volume. The updated algorithms may reduce artefacts due to both motion and due to the presence of metal implants.

The improved image quality of the new CBCT imaging system may allow the use of CBCT images for radiotherapy purposes for which standard CBCT images are not appropriate. Specifically, the use of high-quality CBCT images may enable the anatomic contouring required for radiotherapy treatment planning and the Hounsfield unit accuracy for radiation treatment dose calculation [Giacometti 2020]. This would represent a considerable advance over the CBCT technology currently integrated with treatment machines. High-quality CBCT

images would open possibilities for adaptive radiotherapy and streamlined palliative treatment workflows [Glide-Hurst 2021]. The quality of the CBCT images from this new system will be evaluated in a clinical setting.

This study will evaluate the image quality and Hounsfield Unit accuracy of the new CBCT images, which is necessary to determine the accuracy of radiation dose calculation based on those images. Images of tumours at multiple anatomical locations (head-and-neck, lung (stage I), lung (stage II-IV), left breast, pelvis, and (upper) abdomen) will be acquired and analysed. In addition to the quantitative metrics, images from each anatomical location will be evaluated using different qualitative metrics since higher quality CBCT images may offer different advantages for different anatomical locations.

For head-and-neck images, the expected improvement in visualisation of soft tissue contrast between the tumour, lymph nodes and various organs-at-risk (possibly combined with the reduction of image artefacts caused by metal, e.g., dental implants), together with an extended field of view in both axial and cranial-caudal directions, could allow for the omission of a repeat CT scan that is regularly needed in this patient population for mid-treatment replanning to account for significant changes in the patient anatomy. A CBCT could be captured for treatment replanning purposes without the patient leaving the treatment room and without requiring an additional patient visit.

For images of the thorax, visualisation of small lesions, such as stage I (non-)small cell lung cancer ((N)SCLC), is sometimes difficult in current clinical practice because of the presence of motion artifacts due to breathing. The faster image acquisition of the novel CBCT system (approx. 6 seconds) should allow imaging in a single breath hold for most patients, which should reduce motion artifacts and improve image quality. Also, for lower lobe tumours close to the diaphragm (where diaphragmatic motion compromises image quality), the new CBCT images may provide better visualisation than in current technology for image-guidance.

For advanced stage lung cancer (Stage II-IV), a poor contrast-to-noise ratio (CNR) in the mediastinal region currently hampers proper identification of anatomical structures of interest (e.g., heart, lymph nodes). Improved image quality with improved CNR properties may improve image-guidance procedures for thoracic tumours.

For breast cancer patients, who may have large (nodal) areas that need to be treated, the visualisation of these (nodal) areas on current CBCT systems is hampered by (residual) breathing motion during a breath hold. Also, metal hardware (e.g., surgical clips, expanders) introduce artifacts in the standard CBCT images. The increased FOV, faster image acquisition and newer metal artifact reduction strategies of the novel CBCT system may overcome these problems and improve visualisation.

For the pelvic and (upper) abdominal regions, various tumour sites may be eligible (e.g., bladder, liver, stomach, cervical, prostate, anal and rectal cancer) for inclusion in this study. In

all these tumour sites, artifacts may occur with standard CBCT imaging systems due to long (e.g., 30-60 seconds) CBCT imaging acquisition times. Regions with air-tissue interfaces such as the stomach, intestines, and rectum are known to cause image artifacts with standard CBCT systems. Faster image acquisition with the novel CBCT system (approx. 6 seconds) reduces the likelihood of (residual) motion during the scan. Improved soft-tissue characterisation may improve visualization of individual structures in this anatomical region. Furthermore, metal artifact reduction strategies of the novel CBCT system may improve visualization of structures in the pelvis in patients with hip implants, which lead to severely decreased image quality in standard CBCT images.

2. OBJECTIVES

Primary Objective:

- Describe the differences in quality of CBCT images acquired with the novel cone-beam CT imaging system to the quality of standard cone-beam CT images used for image-guidance and to that of conventional CT images used for radiotherapy planning purposes.

Secondary Objectives:

- Evaluate the suitability of the novel CBCT images for radiation dose calculation.
- Obtain qualitative assessments of novel CBCT vs. standard cone-beam CT images (if available) from the perspectives of radiation oncologists and radiation therapists for the use of the CBCT images in image guidance and planning.
- Obtain qualitative assessments of breath hold CBCT vs. free breathing cone-beam CT images (for patients receiving a breath hold and a free breathing CBCT) or of fast CBCT acquisition vs. slow CBCT acquisition (for patients receiving a 6-second and a 60-second CBCT) for the use of the CBCT images in image guidance and planning.

3. STUDY DESIGN

Single arm, non-randomized, prospective study.

4. STUDY POPULATION

4.1 Population (base)

The population being investigated are patients referred to Maastro for external beam photon radiation treatment.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- The patient will be treated with external beam photon radiotherapy at Maastro for head-and-neck cancer, stage I lung cancer, stage II-IV lung cancer, left breast cancer, or tumours in the abdominal or pelvic region.
- Age ≥ 18 years

- Ability to understand the requirements of the study and to give written informed consent, as determined by the treating physician
- Provision of written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patient is pregnant

4.4 Sample size calculation

This study is being performed to generate initial quality and suitability assessments for a novel cone beam CT imaging system. The study design does not involve any intervention in the subject's cancer care.

Endpoints are based on the comparison of image quality produced by the novel cone-beam CT imaging system to that of standard cone-beam CT imaging and to conventional CT images used for radiotherapy planning purposes. Image quality is determined from Contrast-to-Noise Ratio (CNR) for a Region of Interest (ROI) and a Reference (REF). The specific ROI and REF depend on the tumour site that is scanned (see Chapter 10.1). Therefore, the expected mean difference and variation for CNR are unclear up front and no single assumption for a minimum difference and standard error can be selected. The sample size calculation will be based on effect size of the CNR for a paired samples T-Test. With this method, no assumptions have to be made on the exact difference and variation. 40 subjects will be enrolled with a minimum of 5 patients per each of the six target anatomical locations (head-and-neck, stage I lung cancer, stage II-IV lung cancer, left breast, pelvic and abdomen), which will provide sufficient data for initial assessments to be performed in each anatomical location. A sample of 40 patients is sufficient to determine differences between means for related samples with an effect size of 0.45. This is between a small and medium effect size [Cohen 1988]. In order to attain sufficient variability in patient shape, size and distribution of anatomical structures, a minimum of 5 patients per each of the six target areas (head-and-neck, stage I lung cancer, stage II-IV lung cancer, left breast, pelvic and abdomen) will be included in the study.

5. TREATMENT OF SUBJECTS

Not applicable as no treatment of patients will be delivered on the new Halcyon 4.0 system. Patients will receive regular treatment in Maastro using the standard clinical equipment and procedures.

5.1 Investigational product/treatment

An investigational product is used (see Chapter 6), no treatments are performed using the investigational product.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Halcyon 4.0

6.2 Summary of findings from non-clinical studies

No pre-clinical (animal) testing of the novel CBCT imaging system was performed because it is standard practice to verify dose and image quality using head and body phantoms. Information about the pre-clinical testing for safety and conformity is presented in Section 6 (Product verification and validation) of the Investigational Medicinal Product Dossier (IMDD) checklist, which is attached to this clinical trial protocol.

6.3 Summary of findings from clinical studies

There are no results or findings from clinical studies currently available.

6.4 Summary of known and potential risks and benefits

Information about the benefit-risk analysis and the risk management for the novel CBCT imaging system is provided in Section 5 (Benefit-risk analysis and risk management) of the Investigational Medicinal Product Dossier (IMDD) checklist, which is attached to this clinical trial protocol.

6.5 Description and justification of route of administration and dosage

Not Applicable.

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Investigational Medicinal Product

Not Applicable.

6.8 Drug accountability

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Primary objective: Describe the differences in image quality produced by the novel cone-beam CT imaging system to the quality of standard cone-beam CT imaging and to that of conventional CT images used for radiotherapy planning purposes. For this

objective, the image contrast-to-noise ratio (CNR) will be evaluated. CNR is frequently used to measure image quality.

8.1.2 Secondary study parameters/endpoints

Secondary objective: Evaluate the suitability of the novel CBCT images for radiation dose calculation.

For this objective, targets and organs at risk will be delineated on the novel CBCT images acquired for each subject. The treatment plan created for the patient on the planning CT scan will be registered to the novel cone-beam CT dataset, the dose will be recalculated on the standard CBCT (if available) as well as the novel cone-beam CT. The delineations of target and OARs will either be copied, deformed or manually delineated on the CBCT images, the radiotherapy dose metrics for specific structures relevant for the anatomical site that is imaged will be compared to dose metrics from the original treatment plan.

Secondary objective: Qualitative assessment of novel CBCT vs. standard cone-beam CT imaging system by radiation oncologists and therapists.

Qualitative assessment of the novel CBCT images will be obtained by presenting individual novel CBCT images as well as head-to-head comparisons of novel and standard CBCT images from the same patient. At least 2 radiation oncologists and 2 radiation therapists will be asked to rank the suitability of the images for image guided radiotherapy and for treatment planning on a 5-point Likert scale, with specific assessments for each of the anatomical locations included in the study:

- Head and neck: contrast between tumour and organs at risk; sufficiency of imaging volume, reduction in metal artifacts (where applicable)
- Lung cancer (stage I): Identification and delineation of the tumour
- Lung cancer (stage II-IV): Identification of structures of interest in the mediastinal region (organs-at-risk, primary tumour and possible involved lymph nodes).
- Left breast cancer: Identification and delineation of structures of interest; sufficiency of imaging volume; reduction in metal artifacts (where applicable).
- Abdominal cancers: Identification and delineation of structures of interest; reduction in air/tissue interface artifacts.
- Pelvic cancers: Identification and delineation of structures of interest; reduction in air/tissue interface artifacts; reduction in metal artifacts (where applicable).

Secondary objective: Qualitative assessment will be performed for the patient categories receiving 2 different novel CBCT imaging modes. Stage II-IV lung cancer patients stage (II-IV) receive a 60 seconds free breathing CBCT acquisition and a 6 seconds breath hold CBCT acquisition. Breast, stage I lung cancer stage I and abdominal cancer patients receive a 6 seconds breath hold and a 6 seconds free-breathing CBCT acquisition. A head-to-head comparison of image quality between the 2 modes of novel CBCT image acquisition will also be performed. At least 2 radiation oncologists and 2 radiation therapists will be asked to rank the suitability of

the images for RT image guidance and for treatment planning on a 5-point Likert scale, with specific assessments for each of the anatomical locations included in the study (as defined in previous secondary endpoint).

In all analyses where a novel CBCT is compared to a standard CBCT, the standard CBCT will be taken from the subject's radiation treatment fraction that was delivered on the same day as the novel CBCT image acquisition. Therefore, the only additional imaging is the novel CBCT.

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

No randomisation will be performed.

8.3 Study procedures

Patients will be recruited from the standard radiotherapy population. Patients will be asked to undergo an additional imaging session on the novel cone-beam CT imaging system during which 1 or 2 additional CBCT images will be acquired. The additional imaging session will be performed on one of the subject's standard treatment days to limit additional travel and burden on the patients.

The exact technical details of the additional imaging session depend on the anatomical region to be investigated, as described below.

For head-and-neck patients: one additional extended cone-beam CT scan will be performed. The extended CBCT consists of (typically 2) sequential cone-beam CT scans that are automatically stitched together to create a full field-of-view of the treated region.

For stage I lung cancer patients: two additional cone-beam CT scans will be acquired. The first cone-beam CT scan will be performed under conditions of free-breathing. An additional cone-beam CT scan will be acquired with the subject performing a breath hold.

For stage II-IV lung cancer patients: two additional cone-beam CT scans will be acquired. Both cone-beam CT scans will be performed under conditions of free-breathing. The first cone-beam CT will be a fast (6 second) cone-beam CT. The second CBCT will be a slow scan (approximately 60 seconds in duration) that will be used to evaluate novel motion compensation algorithms.

For left breast cancer patients: one additional breath hold cone-beam CT scan will be acquired.

For pelvic cancer patients: one additional cone-beam CT scan will be acquired under conditions of free breathing.

For abdominal cancer patients: two additional cone-beam CT scans will be acquired. The first cone-beam CT scan will be performed under conditions of free-breathing. An additional cone-beam CT scan will be acquired with the subject performing a breath hold.

All cone-beam CT scans will be acquired using the vendor-supplied default imaging mode for the anatomical region being imaged.

8.4 Withdrawal of individual subjects

Subjects can withdraw from the study at any time for any reason if they wish to do so. The decision to withdraw from the study will not result in any consequences for the subject. The investigator can decide to withdraw a subject from the study if the investigator decides that continuation in the study may be harmful to the subject. Data collected until the time of withdrawal will be used for analysis, unless the patient requests that the data is destroyed.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Subjects who withdraw before their novel CBCT imaging session has occurred will be replaced by new subjects as long as the inclusion numbers are not exceeded.

8.6 Follow-up of subjects withdrawn from treatment

No follow-up is foreseen after withdrawal.

8.7 Premature termination of the study

Premature termination of the study will occur if:

- The approval of the competent medical ethics review committee that assessed the research is irrevocably withdrawn;
- It appears that the continuation of the research cannot serve a scientific purpose, and this is confirmed by the medical ethics review committee that had given a positive assessment of the research;
- The principal investigator is no longer able to perform the duties of the principal investigator, and no substitute can be found by mutual consent.
- The Sponsor decides to end the study early.
- It can be reasonably concluded that the study must be terminated in the interests of the health of the study subjects.
- The Sponsor and/or the Institution become or are declared insolvent or a petition in bankruptcy has been filed against one of them or if one of them is dissolved
- Circumstances beyond a party's control occur that render continuation of the study unreasonable.

- One of the parties fails to comply with the obligations arising from the CTA and, if capable of remedy, is not remedied within 30 days after receipt of written notice from the other party specifying the non-compliance and requiring its remedy, unless failure to comply is not in reasonable proportion to the premature termination of the study.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient grounds to believe that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt, including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will ensure that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

An adverse event, per ISO 14155:2020, is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

All adverse events that are reported spontaneously by the subject or observed by the investigator or his staff, and that the investigator judges to be possibly, probably or definitely related to the acquisition of the novel CBCT images will be recorded in the study database.

9.2.2 Serious adverse events (SAEs)

A serious adverse event, per the CCMO, is any untoward medical occurrence or effect that results in:

a) death;
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    1) a life-threatening illness or injury (at the time of the event), or
    2) a permanent impairment of a body structure or a body function including chronic diseases, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment.

d) any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

Items a), b), and c) are aligned with the ISO 14155:2020 definition of a Serious Adverse Event.

Note that planned hospitalization for a pre-existing condition, or a procedure required by this protocol without serious deterioration in health, is not considered a serious adverse event.

Study staff are required to notify the Principal Investigator of any serious adverse event (SAE) experienced by a subject while that subject is enrolled in the study. SAEs that the investigator judges as possibly, probably or definitely related to the acquisition of a novel CBCT image must be reported to the study sponsor within 24 hours of becoming aware of the event.

Sponsor contact for AE reporting:
Sean Davidson
Phone: +1 (437) 991-8294
Email: sean.davidson@varian.com

The local principal investigator or an authorized delegate will report the SAE to the sponsor within 24 hours delay after obtaining knowledge of the event. The local principal investigator or an authorized delegate will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol. An initial notification of SAEs that result in death or are life threatening will be made within 7 days of first learning about the SAE, with a complete preliminary report submitted within at most an additional 8 days. All other SAEs will be reported within a period of at most 15 days after the local investigator has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

The sponsor will submit, once a year throughout the clinical trial, or as part of the final report if the trial takes less than a year to complete, a safety report to the accredited METC.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. Recording of AEs

is required during the period that a subject participates in the study. A subject's participation ends with the additional novel CBCT acquisitions.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

A DSMB or safety committee is not deemed applicable for this study.

10. STATISTICAL ANALYSIS

Analysis will include all patients that provided informed consent and completed the novel cone beam CT imaging. In general, analyses will depend upon the type of data. Categorical data will be described using proportions and 95% confidence interval and differences will be tested using Chi-square analyses. Means, standard deviations and 95% confidence interval will be calculated for continuous parameters which are normally distributed and differences will be analysed using T-tests or analysis of variance. In case variables violate the normality distribution, medians, interquartile range, minimum and maximum will be reported and the appropriate non-parametric alternative for T-tests and analysis of variance will be used.

10.1 Primary study parameter(s)

Primary objective: Describe the differences in image quality produced by the novel cone-beam CT imaging system to the quality of standard cone-beam CT imaging and to that of conventional CT images used for radiotherapy planning purposes. To quantify image contrast-to-noise ratio (CNR) every image acquired for each subject will be analysed. Contrast-to-noise ratio (CNR) will be quantified using the following equation:

$$CNR = (|\langle HU_{ROI}\rangle - \langle HU_{REF}\rangle|) / (SD_{ROI}^2 + SD_{REF}^2)^{0.5}$$

where $\langle HU_{ROI}\rangle$ and $\langle HU_{REF}\rangle$ are the mean Hounsfield Units (HU) in a region of interest and referenced (background) region, respectively, with SD_{ROI} and SD_{REF} the corresponding standard deviations of the HU values in those regions.

The ROI and REF are defined for every tumour site individually. For the head-and-neck cohort this will be the tumour region (ROI) and a proximal muscle tissue for reference (REF). For lung cancer (both stage I and II-IV), the gross tumor volume will be defined as ROI, and a proximal muscle or fat tissue will serve as the reference (REF). For the left-sided breast cancer, the breast tissue is the ROI, with a proximal muscle or fat tissue as the reference. For abdominal and pelvic case, the tumour volume is the ROI, with a proximal muscle or fat tissue

Difference in CNR will be tested using a paired samples T-Test for which the hypothesis is that there is a difference in CNR between the novel CBCT imaging system and standard cone-beam CT/conventional planning CT imaging. A p-value lower than 0.05 (Bonferroni corrected p-value lower than 0.025) will be assumed to be statistically significant.

10.2 Secondary study parameters

Secondary objective: Evaluate the suitability of the novel CBCT images for radiation dose calculation. For this objective, targets and organs at risk will be delineated or propagated

from the planning CT scan on the standard CBCT and novel CBCT images acquired for each subject. The treatment plan created for the patient on the planning CT scan will be registered to both the CBCT acquired during the standard treatment of the patient (if available) and the novel cone-beam CT dataset. The dose will be recalculated on the standard CBCT and the novel cone-beam CT and the radiotherapy dose metrics for specific structures relevant for the imaged tumour location will be compared to dose metrics from the original treatment plan. The standard CBCT will be taken from the patients' radiation treatment fraction delivered on the same day (if available) as the novel CBCT image acquisition. Dose Volume Histogram (DVH) parameters will be extracted using the commercially available treatment planning system (Varian Eclipse).

Secondary objective: Qualitative assessment of novel CBCT vs. standard cone-beam CT imaging system from radiation oncologists and therapists. Qualitative assessment of the novel CBCT images will be obtained by presenting individual novel CBCT images as well as head-to-head comparisons of novel and standard CBCT images from the same patient (if available). At least 2 radiation oncologists and 2 radiation therapists will be asked to rank the suitability of the images for RT image guidance and for treatment planning on a 5-point Likert scale, with specific assessments for each of the anatomical locations included in the study.

Besides a rating of the image quality in terms of overall quality impression, specific questions will be tailored for the different anatomical areas:

- Head and neck: contrast between tumour and organs at risk; sufficiency of imaging volume; reduction of artifacts (e.g., due to dental fillings), where applicable.
- Lung cancer (stage I): Identification and delineation of the tumour
- Lung cancer (stage II-IV): Identification of structures of interest in the mediastinal region (organs-at-risk, primary tumour and possible involved lymph nodes).
- Left breast cancer: Identification and delineation of structures of interest; sufficiency of imaging volume; reduction in metal artifacts (where applicable).
- Abdominal cancers: Identification and delineation of structures of interest; reduction in air/tissue interface artifacts.
- Pelvic cancers: Identification and delineation of structures of interest; reduction in air/tissue interface artifacts; reduction in metal artifacts (where applicable).

Secondary objective: Qualitative assessment will be performed for the patient categories receiving 2 different novel CBCT imaging modes. Stage II-IV lung cancer patients stage receive a 60 seconds free breathing and a 6 seconds breath hold CBCT acquisition. Breast, stage I lung cancer and abdominal cancer patients receive a 6 seconds breath hold and 6 seconds free-breathing CBCT acquisition. A head-to-head comparison of image quality between the 2 modes of novel CBCT image acquisition will also be performed. At least 2 radiation oncologists and 2 radiation therapists will be asked to rank the suitability of the images for RT image guidance and for treatment planning on a 5-point Likert scale, with specific assessments for each of the anatomical locations included in the study (as defined

in previous secondary endpoint).No statistical tests are planned for these secondary endpoints. Comparisons will be based on descriptive statistics and calculation of 95% confidence intervals.

10.3 Other study parameters

Not applicable.

10.4 Interim analysis (if applicable)

Not applicable.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version date 19th October 2013), in accordance with the Medical Research Involving Human Subjects Act (WMO) and in accordance with the Medical Device Regulation (EU) 2017/745 (MDR, article 82).

11.2 Recruitment and consent

Potential participants will be identified by the Trial Physician Assistant (TPA), a process that is embedded in the standard clinical patient workflow at Maastro. When a patient is identified as a potential participant and meets all inclusion and exclusion criteria, the treating physician will inform the patient about the study and will provide the patient with the written patient information and informed consent that has been prepared and approved for the study. The treating physician will give the patient a brief explanation of the study ask the patient for permission to contact them about the study.

Informed Consent procedure will be conducted conforming Article 63 of the MDR. If the patient agrees to be contacted about the study, the TPA will provide the patient with additional information about the clinical trial and will answer any questions the patient may have. If the patient will not visit Maastro before the start of the study, the TPA will provide the patient with all the information and will answer questions the patient may have by phone. If, after reading the written patient information and informed consent, the patient has additional questions, the patient can contact the TPA who informed the patient about the study. The patient can also contact the independent physician for this study with their questions. The contact details for all these persons are included in the informed consent document that is provided to the patient.

The recruitment will take place at Maastro. The patient will have at least 3 days of time to consider participation in the trial, however a period much longer than 3 days will interfere with normal clinical workflows and risk delaying urgently needed treatment. Therefore, the subject will be contacted after 3 days by the TPA. The TPA will ensure that the patient understands the content of the study, that all the patient's questions are answered, and the patient is willing to participate in the study. The TPA will verify whether the patient

understands what participation in the trial entails by asking them to repeat in their own words what the participation means. If the patient decides to participate in the trial, they will give verbal consent to plan the additional scan. Prior to this scan, an appointment will be planned for the patient and TPA to discuss any questions of the patients regarding the trial and to sign the Informed Consent form. The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

The written and verbal versions of the Participant Information and Informed Consent that are presented to the participants will detail no less than: the exact nature of the trial; what participation in the trial will involve for the participant; the implications and constraints of the protocol and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Written Informed Consent will then be obtained by means of a dated participant signature and a dated signature of the person who presented and obtained the Informed Consent. The TPA will, together with the clinical trial coordinator, ensure that the informed consent is correctly and fully signed and dated by the participant and included in the study documentation at the research department of Maastro before any study-related procedures take place. The person who obtains the consent must be suitably qualified and experienced and have been authorized to do so by the Principal Investigator. The participant will also receive an original of the signed informed consent form. The signed form will be retained at the trial site.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

Additional imaging is performed on the novel cone-beam CT imaging device using x-rays. There is no direct benefit for the individual patients. Additional radiation exposure is only a small fraction (<0.1%) of the radiation received during their standard radiotherapy treatment. Collected data will not be used for clinical decision making. If the novel CBCT images provide new information that may lead to improved treatment, the findings will be communicated to the treating physician but need verification using standard imaging procedures.

11.5 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has a clinical trial insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides coverage for damage to research subjects through injury or death caused by participation in the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

Data processing Varian-Maastro is described within the CTA; various precautions regarding the protection of patient privacy are included in; only deidentified (pseudonomyzed) information will be shared with Varian and legal arrangements are in place using Standard Contractual Clauses for GDPR describing the details of the data processing, transfer and storage of data using encryption methods, rules and roles of MAASTRO and Varian personnel handling the data including user authentication and training, logging and auditing of access.

12.1 Handling and storage of data and documents

A study ID will be attributed to each patient registered in the trial consisting of a sequential inclusion number (i.e. H4GN-MAAS-###). This code will identify the patient and must be included on all case report forms. All data in the study database will be linked to a study ID. Information that could directly identify a patient will not be entered in the database. The study ID will be attributed by Clinical Trial Office (CTO) Maastro. The link between the participant study IDs and their name, unique patient identifier, or other identifying information will be accessible only to delegated Maastro clinical site personnel and will be stored in a secure location at Maastro with limited access. Any paper documents (e.g., worksheets) used in the collection of study data will also be securely stored at the site. Study data will be stored for 15 years on a protected server at Maastro and Varian. The IGJ (Inspectie Gezondheidszorg en Jeugd) and monitors have permission to check all data documents, which will be obtained by CTO Maastro based on the codes for the included patients.

When the participant has signed the informed consent, the participant has given permission that the collected data can be used to answer the research questions of this trial. The patient will be asked to give additional permission for storing and using the data for 15 years for future research projects that are related to CT imaging in cancer patients.

Patient data will be used in accordance with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation, for transfor to Varian (USA based company) dedicated Standard Contractual Clauses ensuring compliance with the EU 2016/679 regulations. Patient data and/or patient material can only leave Maastro in coded form.

Data collected for this study will consist of:

- Case report form data.
- Image data and radiation planning data (target and organ at risk contours, treatment plans, calculated radiation dose distributions).

Case report form data

Case report form data will include

- Basic demographic data (age at consent, sex)
- Information about the anatomical region and type of cancer being imaged
- Medical information relevant to the interpretation of medical images (e.g., the presence of metal implants)
- Information about the acquisition of the images (date, time, imaging parameters) that are collected for the study
- Information about any adverse events or device issues related to the study

Case report form data will be stored in an electronic database provided by a third-party vendor that is contracted by the Sponsor. The database vendor (Cloudbyz) has built their system on top of the Salesforce platform. Study data will be stored in a secure Salesforce data centre located in the United States. All data are encrypted in transit and any data value that can potentially contain personal participant information will be encrypted at rest.

Maastro site personnel who have been delegated responsibility for study data management will be specified on the delegation log and trained by Varian on the study database prior to receiving access to it. Maastro site personnel will access study data via a secure web portal (Cloudbyz Investigator Portal). Individual login credentials (username and password) are provided to each person who will be responsible for data entry. All access and all changes to study data are recorded in an audit log.

Sponsor personnel with responsibilities related to the study will have read-only access to study data. Sponsor access is also linked to individual credentials and requires two-factor authentication. All access to the study database (clinical site and sponsor) is role-based, with permissions defined by a user's role.

Imaging and radiation planning data

The image files collected for the study analyses (novel CBCTs, standard CBCTs and standard CTs used for radiation treatment planning) and the radiation treatment plan data (dose, plan and structure set files) used for the dosimetry analyses, will be exported from the system(s) where they are generated and de-identified. All identifying information will be removed from the image file headers and the patient ID will be replaced with the study ID so that the images can be linked to the correct case report form data and so that images from the same participant can be compared.

Maastro site personnel will upload the de-identified image and radiation treatment plan data generated in this study to a Varian-hosted SharePoint that is physically located in the United States. Access to the SharePoint will be provided via unique web links that are tied to an individual's institutional email address and verified through access codes sent to that email address. Access to the SharePoint will be granted only to site personnel who have

been delegated authorization by the Principal Investigator to manage study data and who have received specific training on SharePoint uploads. Only sponsor personnel with responsibilities related to the study will have access to the de-identified data once it has been uploaded. Sponsor personnel will perform periodic checks of the data that have been uploaded to ensure that it does not contain any identifying information.

Varian personnel will upload de-identified image data from Varian's SharePoint to MeVis Online Academy to conduct the qualitative image assessments specified in this protocol. The MeVis software will be configured to present individual CBCTs or head-to-head comparisons of CBCTs from the same participant to observers (radiation oncologists and radiation therapists). Observers access MeVis Online Academy using individual login credentials and can only see imaging "cases" that are assigned to their account. Sponsor personnel are responsible for managing observer accounts and assigning "cases". The observers will be able to rank the suitability of CBCTs for image guidance and dosimetry planning by answering questions presented by the MeVis software. Only image data will be presented to the observers via MeVis Online Academy (no header information is displayed). Image data will be stored in the MeVis database (physically located in Germany) only long enough for all observers to perform their assessments; image data will be deleted from the MeVis database once the qualitative assessments specified in the protocol are complete.

12.2 Monitoring and Quality Assurance

Regular reviews of case report form data will be performed by the Sponsor Clinical Research Manager or Clinical Data Manager. Data queries will be issued directly from within the study database by sponsor personnel. Maastro clinical site personnel can respond to those queries via the Investigator Portal to the study database.

Monitoring of the study data will be performed onsite on behalf of the sponsor by qualified Maastro monitoring personnel from the Maastro Clinical Trial Office. Maastro monitors will be individuals who are not directly involved in conducting the study. The focus of monitoring activities will be to ensure the rights of the participants are respected, to ensure the study is conducted according to Good Clinical Practice and according to this protocol, and to ensure accurate data collection. Further details will be provided by a Monitoring Plan drafted by the Sponsor.

12.3 Amendments

Amendments are changes that are made to the research after a favourable opinion by the accredited METC has been given. All amendments will be communicated to the METC that provided the favourable opinion of the research.

12.4 Annual progress report

The sponsor will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The sponsor will notify the accredited METC within eight weeks of the end of the study, which is defined as the last participant's novel CBCT imaging session. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The results of the study, whatever they may be, will be presented at international scientific conference(s) and published in peer-reviewed scientific journals by either the clinical site or the sponsor. This will be done in accordance with the CCMO guidelines with regard to publication of research results.

Agreements made in the research contract (Chapter 11) with regard to the 'publication conditions' prevail over the statement(s) made in the research protocol. However, Maastro and Varian have agreed on a policy concerning publication. The publishing party will provide the reviewing party with a proposed publication. The reviewing party will respond within 30 days. When reviewing a proposed publication submitted by the clinical site, Varian may comment on the scientific content of the publication, may make suggestions to improve the clarity of the publication, may request the removal of Varian's confidential information and may request a postponement of publication to allow time to protect proprietary information.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

A full risk analysis of the novel CBCT imaging system has been performed and information about the residual risks can be found in Section 5 of the IMDD checklist.

The additional risks to study participants related to their participation in the study include the small amount of additional ionizing radiation received from the extra 1-2 novel CBCT images acquired during this study. As mentioned previously in this document, the amount of additional radiation is very small compared to the radiation doses these participants are receiving for their cancer treatment. The additional dose received from acquisition of a novel CBCT is equivalent to the dose received from a standard CBCT acquisition, which is performed at least once every treatment fraction in standard care. The additional dose from the novel CBCT is unlikely to result in additional harm to the participants.

Participation in the trial also includes additional risk of a privacy breach created by the collection of data for the study. This risk will be minimized by collecting only the minimum amount of data required to conduct the analyses specified in this study, by linking study data to study IDs and removing any information that could directly identify the subject, and by restricting access to the study data to those individuals with defined responsibilities in conducting the study.

The mechanism of action of CBCT imaging is well understood and there are no adverse effects expected from 1-2 additional CBCT images. A search of international medical device databases shows no recalls or serious adverse events within the last four years that are related to previous versions of the CBCT imaging system and radiation treatment platform, indicating that the system has a strong safety record. The new imaging system has been characterized as much as possible through the use of standardized phantoms. The purpose of this study is to evaluate the suitability of the images in a clinical setting, which requires acquiring images of human patients who are being treated with radiation therapy.

13.2 Synthesis

The results from this study have the potential to benefit future patients undergoing radiation treatment for cancer or other malignant conditions. Participation in the study is not expected to result in direct benefits to the participants. The higher image quality that is anticipated in the novel CBCT imaging system may result in findings that may improve a participant's treatment but such findings must be confirmed by conventional imaging; no clinical decisions will be made from the novel CBCTs acquired during this study.

The residual risks from the novel imaging system and the risks from participation in the study are low and have been reduced as low as reasonably achievable. On balance, the benefits from the study outweigh the risks.

14. REFERENCES

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