CLINICAL INVESTIGATION PLAN (CIP)

Reducing Cardiac Radiation Dose in CPAP-assisted Radiotherapy in Breast Cancer: a Prospective Non-Randomized Clinical Trial

CPAP-assisted Radiotherapy in Breast Cancer

Version number: v1.5 *68702* – Date *11/04/2025*

Clinical Investigation number: *S68702*

Single Identification Number (SIN): *[SIN Nr]*

Sponsor

University Hospitals Leuven (UZ Leuven)

Herestraat 49, B-3000 Leuven

Coordinating Investigator

Prof. Dr. Caroline Weltens

(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)

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LIST OF PARTICIPATING SITES

(if applicable)

List Of Participating Sites	Principal Investigator
University Hospitals Leuven (UZ Leuven)	Prof. Dr. Caroline Weltens

SIGNATURES

Title: Reducing Cardiac Radiation Dose in CPAP-assisted Radiotherapy in Breast Cancer: a Prospective Non-Randomized Clinical Trial

CIP: CPAP-assisted Radiotherapy in Breast Cancer

The undersigned confirm that the following CIP has been acknowledged and accepted and that they agree to conduct the Investigation in compliance with the approved CIP (and any subsequent amendments if applicable) and will adhere to the principles outlined in the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., the EU Medical Device Regulation 2017/745 (MDR), EU General Data Protection Regulation 2016/679 (GDPR)) and ISO 14155:2020), the appropriate local legislation(s) and all other applicable legal and regulatory requirements as amended. The most stringent requirements, guidelines or regulations must always be followed.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the Investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Investigation publicly available through publication or other dissemination tools, in accordance with this CIP without any unnecessary delay and that an honest accurate and transparent account of the Investigation will be given; and that any discrepancies from the Investigation as planned in this CIP will be explained.

Coordinating Investigator

Prof. Dr. Caroline Weltens

.....	.....	.....
Name & Title	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

Prof. Dr. Caroline Weltens

.....	.....	.....
Name & Title	Signature	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
BC	Breast Cancer
CA	Competent Authority
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CM	Concomitant Medication
CPAP	Continuous Positive Airway Pressure
CT	Computed Tomography
DD	Device Deficiency
DIBH	Deep Inspiration Breath Hold
DMP	Data Management Plan
Dmax	Maximum radiation dose a specific organ at risk is receiving (expressed in Gy)
Dmean	Mean radiation dose a specific organ at risk is receiving (expressed in Gy)
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EUDAMED	European Database for Medical Devices
FB	Free Breathing
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	EU General Data Protection Regulation 2016/679
Gy	Gray, unit of radiation dose
IB	Investigator's Brochure
ICF	Informed Consent Form
IFU	Instructions For Use
IMD	Investigational Medical Device
IMRT	Intensity Modulated Radiotherapy
ISF	Investigator Site File

IUD	Intrauterine devices
LPLV	Last Patient Last Visit
MBC	Multidisciplinary Breast Centre
MDR	EU Medical Device Regulation 2017/745
MHD	Mean Heart Dose
MSP	Median Supraclavicular Parasternal
NTCP	Normal Tissue Complication Probabilities
OAR	Organs At Risk
OSAS	Obstructive Sleep Apnea Syndrome
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
PT	Proton Therapy
RNI	Regional Nodal Irradiation
RT	Radiotherapy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIN	Single Identification Number
SOP	Standard Operating Procedure
TMF	Trial Master File
TNM	Tumor-Node-Metastasis
VMAT	Volumetric Modulated Arc Therapy
VXGy	Volume of the organ at risk receiving X Gy radiation dose (expressed in %), e.g. V5Gy of the heart is the volume of the heart receiving 5 Gy radiation dose (expressed in %).

FUNDING AND THIRD PARTIES

Funder or service provider	Type of Support
Myny-Vanderpoorten Fonds	Financial support
AIR LIQUIDE MEDICAL nv - VitalAire	Grant for acquisition of essential CPAP equipment solely

No additional travel reimbursement or other compensation is foreseen for the Investigation participants, because travel reimbursement is already provided for radiotherapy patients in standard of care.

ROLES AND RESPONSIBILITIES

The Principal Investigator (PI) is responsible for the conduct of the Investigation at her Participating Site, and for protecting the rights, safety and well-being of the participants. As such the PI must ensure adequate supervision of the Investigation conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom she has delegated specified Investigation-related duties. The PI will ensure that adequate training is provided and documented for all Investigation staff, prior to conducting assigned Investigation-related activities.

It is the CI's responsibility to supervise the general conduct (e.g., study progress, communication, CIP training and support of the participating sites, annual reporting to the EC, end of Investigation notification(s) and results reporting…) of the Investigation. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in ISO 14155:2020 and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

CIP SYNOPSIS

Title of clinical Investigation («Investigation»)	Reducing Cardiac Radiation Dose in CPAP-assisted Radiotherapy in Breast Cancer: a Prospective Non-Randomized Clinical Trial
CIP Short Title Acronym	CPAP-assisted Radiotherapy in Breast Cancer
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Prof. Dr. Caroline Weltens
Contact Address CI	Herestraat 49, 3000 Leuven
Contact Email CI	caroline.weltens@uzleuven.be
Contact Phone CI	016 347665
SIN number	[SIN Nr]
Other public database number	Not Applicable
Medical condition or disease under investigation	Breast Cancer
Study rationale	Decreasing cardiac radiation doses by using a continuous positive airway pressure (CPAP) device during radiotherapy (RT) for breast cancer (BC) patients
Primary objective	To demonstrate a decrease of approximately 0.5 Gy Mean Heart Dose (MHD) by using CPAP-assisted RT compared to the standard protocol in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)).
Secondary objective(s)	- To compare target volume coverage between standard and CPAP-assisted RT in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI (<70y/o) and left-sided with RNI (70-80 years old)) - To determine which patients benefit the most from CPAP-assisted RT based on dosimetric outcomes for different organs at risk (OAR) in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)): o Whole heart o Cardiac substructures (large vessels, atria, ventricles, valves, conduction nodes, coronary arteries, coronary artery calcifications, heart base) o Lungs o Ipsilateral lung o Contralateral breast o Liver - To determine patient comfort and tolerance of CPAP-assisted RT by analysing patient questionnaires - To compare reproducibility and accuracy between standard and CPAP-assisted RT by using surface scanning and daily cone beam CT (CBCT) parameters - To compare DIBH performance between standard and CPAP-assisted RT for left-sided BC by using surface scanning and daily CBCT parameters

	- To compare time-effectiveness between standard and CPAP-assisted RT
	  o Set-up time
	  o Matching time
	  o Radiation time
	- To compare cost-analysis between standard and CPAP-assisted RT
	- To compare normal tissue complication probabilities (NTCP) from various NTCP models (Darby et al. and models developed in study s68508) between standard and CPAP-assisted RT

Clinical Investigation Design	Prospective Non-randomized Clinical Trial

Endpoints	Primary endpoint: Difference in MHD in Gy between standard and CPAP-assisted RT in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):
	Secondary endpoints:
	- Differences in target volume coverage between standard and CPAP-assisted RT in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):
	- Differences in OAR dosimetric parameters between standard and CPAP-assisted RT in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):
	  o Whole heart
	  o Cardiac substructures (large vessels, atria, ventricles, valves, conduction nodes, coronary arteries, coronary artery calcifications, heart base)
	  o Lungs
	  o Ipsilateral lung
	  o Contralateral breast
	  o Liver
	  o
	- Likert scale scores from patient questionnaires
	- Differences in mean deviation of surface, OAR and target volume positions per fraction (in mm) in standard vs CPAP-assisted RT (reproducibility: day-to-day variation in surface, OAR and target volume position)
	- Differences in average surface, OAR and target volume maximum shift observed during each fraction (in mm) in standard RT vs CPAP-assisted RT (accuracy: difference of daily surface, OAR and target volume position versus planning position)
	- Differences in RT duration between standard and CPAP-assisted RT (minutes)
	  o Set-up time
	  o Matching time
	  o Radiation time
	- Differences in DIBH duration between standard and CPAP-assisted RT (seconds)
	- Differences in total treatment costs between standard and CPAP-assisted RT (euro)

	- Differences in normal tissue complication probabilities (NTCP) from various NTCP models (Darby et al. and models developed in study s68508) between standard and CPAP-assisted RT
Sample Size	73 patients (Approximately 83 participants will be screened to achieve an estimated total of 73 evaluable participants.)
IMD	CPAP device
Comparator device(s)	Not Applicable
Maximum duration of treatment and Follow Up of a Participant	4-5 weeks
Anticipate First Patient First Visit (FPFV)	01-02-2025
Anticipate Last Patient Last Visit (LPLV)	01-02-2026

STUDY FLOWCHART

Schedule of Events – Study specific Procedures / Assessments

Please indicate in the flowchart with different colors whether a procedure is performed as part of the standard of care or specifically for the Investigation.

1 : Informed Consent process should take place prior to all other study-related procedures at the screening visit
2 : …

Procedures/ Assessment	**Screening**		**Treatment period**		
Visits / Contacts	Visit 1 Consultation	Visit 2 CT Simulation	Visit 3-18 Radiation Treatment	End of Treatment period / Early Termination	Unscheduled Visit
Timing (weeks)		0	[2]		
Visit Window (days)	-28 to -1		±[14-35] days	± [35] Days	
Informed consent	X [1]				
Inclusion / Exclusion criteria	X				
Demographics	X				
Medical history	X				
Cardiovascular risk profile (through questionnaires)	X				
Physical examination	X				
Use of investigational device		X	X (when CPAP-assisted RT is chosen as treatment of choice)		
Radiological Assessments (CT) without CPAP		X			
Radiological Assessments (CT) with CPAP		X			
Patient experience questionnaire		X	X (every 7 days when CPAP-assisted RT is chosen as treatment of choice)		
Reason for discontinuation				(X)	
(Serious) Adverse event (S)(AE) assessment	X	X	X	X	X
Concomitant Medication (CM)	X				

1 Background and Rationale

Breast cancer (BC) remains the most prevalent cancer in women worldwide with the highest mortality rate among all female cancers in Europe and second highest mortality rate among all female cancers in the United States of America [1,2]. Despite it being the most common cancer in women with a persistent rising incidence, the overall prognosis is already relatively good with a 5 year overall survival (OS) of approximately 80-90% in the Western world and these numbers still seem to improve because of earlier diagnosis and more recent advances in treatment strategies [1]. Because of these long-term survivors, it is becoming increasingly important to strive for a high quality of life after BC curation. Therefore, toxicity following different treatment modalities becomes a crucial part of BC research.

Adjuvant local / locoregional radiotherapy (RT) has proven to increase OS and local control rates after breast conserving surgery (BCS) and also after mastectomy in some more advanced clinical cases [3,4]. Therefore, approximately 70% of BC patients are treated with adjuvant RT as a crucial component of curative treatment [5]. However, it is important to note that radiation treatment in the thoracic region is also known to be potentially cardiotoxic, particularly after a long latency period of more than 10 years (although earlier cardiotoxicity has also been reported).

BC patients treated with RT had a 1.76-fold (95% confidence interval: 1.34 to 2.31) higher risk of dying of cardiac disease than those who did not receive RT [6]. Various cardiac conditions have been associated to radiation injury. Most importantly heart failure, ischemic cardiac disease and atrial fibrillation have been reported after BC RT, but association with pericardial disease, arrhythmia and cardiac death have also been demonstrated [7–20]. As a result, research on radiation-induced cardiotoxicity has become a significant focus within the field of breast cancer research, aiming to minimize treatment-related cardiac toxicity.

In the past, various studies reported a dose-response relationship for radiation-induced cardiac toxicity. Not only mean heart dose (MHD) but also radiation doses to cardiac substructures such as coronary arteries and the ventricles for example have been associated with increased risk of developing cardiac adverse events [7,20–29]. On the other hand, patient-related characteristics such as pre-existing cardiac risk factors also play an important role [30,31].

To reduce radiation-induced cardiac toxicity numerous cardiac-sparing RT techniques have been developed in the past years, such as modern RT techniques (Intensity Modulated Radiotherapy (IMRT)/ Volumetric-Modulated Arc Therapy (VMAT)), deep inspiration breath hold (DIBH), prone RT and lately the use of proton therapy has also been investigated in this perspective [32–38]. Since these techniques have shown obvious cardiac dose reductions, several investigations have been initiated to fine-tune and optimize them, potentially reducing cardiac doses even further. For example, prone and DIBH radiotherapy have been combined together showing dosimetric advantages [39–42]. Moreover, various respiration-assisting devices have been investigated for their role in facilitating DIBH, not only to improve dosimetry parameters but also to enhance accuracy, reproducibility, and ultimately, patient comfort. For example, the use of mechanically assisted ventilation in DIBH has been shown to deliver high irradiation accuracy while better protecting the organs at risk (OAR) [43]. In a small retrospective study the use of a continuous positive airway pressure (CPAP) device has also been investigated in combination with DIBH in left-sided BC patients showing clear dosimetric advantages on cardiac radiation doses [44]. Additionally, some smaller retrospective and non-randomized prospective studies also showed decreased cardiac doses when CPAP was used in a free breathing (FB) setting, for example in patients not able to perform DIBH [45–49]. The same CPAP-assisted strategy has been investigated in RT for other thoracic malignancies showing similar results confirming larger lung volumes and some also demonstrating decreased cardiac doses with CPAP [50–52]. These potential dosimetric advantages with CPAP could be a consequence of combined increased lung volume and also inferior displacement of the heart, resulting in a larger distance between the heart and the RT target volume. In summary, preliminary evidence and proof of concept indicating potential advantages of using CPAP in BC RT already exists from small, mostly retrospective studies. This makes CPAP a promising technique deserving further exploration through large-scale and prospective investigations. For example, there is currently no data on the potential benefits of CPAP in patients with right-sided breast cancer, and critical factors such as patient compliance, accuracy, and stability need assessment before implementation of CPAP in clinical practice.

The aim of this specific study is thus to prospectively confirm and investigate the potential benefits of CPAP in optimizing RT for BC patients and assess its clinical performance in daily radiation oncology practice.

In this study, each patient will undergo an initial CT simulation scan according to the standard protocol (without CPAP support), followed by another CT simulation scan with CPAP respiratory assistance. For right-sided BC patients standard protocol implies Free Breathing conditions. For left-sided BC patients standard protocol covers CT in Deep Inspiration Breath Hold (DIBH), except for patients unable to perform DIBH or older than 70 years old, these will use Free Breathing as standard protocol. In the further course of the protocol, the term 'standard RT' will be used to denote these configurations. The second scan thus includes a CPAP-assisted Free Breathing for right-sided BC patients and left-sided BC patients unable to perform DIBH. In the left-sided BC group the second CT scan covers a CPAP-assisted DIBH. These configurations are further referred to as 'CPAP-assisted RT'. A dedicated medical radiation physicist or dosimetrist will then make radiation plans for both scenarios. The radiation oncologist will then evaluate both plans, selecting the one with the most favorable dosimetric results for the effective irradiation of the patient.
This study will be different than previously published work in various ways. Firstly, we will not only include patients with left-sided BC, but also right-sided BC patients will be included, more specifically right-sided BC patients who require a locoregional radiation treatment including RT of the elective regional lymph node regions (e.g. median supraclavicular region, internal mammary nodes and/or axillary lymph nodes). In these patients, maintaining cardiac and pulmonal radiation doses bellow generally accepted dose constraints can be challenging. Therefore, radiation oncologists often partially omit radiation of the regional lymph nodes to reduce cardiac and pulmonal doses, possibly resulting in more oncological failure. Using CPAP assisted RT in these patients could potentially improve radiation dosimetry, consequently improving the quality of radiation treatment and, in turn, potentially leading to improved oncological outcomes. Secondly, we will investigate which BC patients benefit the most from CPAP assisted RT by comparing dosimetric results in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):. Thereafter, patient compliance and tolerance of CPAP assisted RT will be assessed using patient questionnaires. Accuracy, reproducibility and DIBH performance of CPAP-assisted RT will also be studied by using data from the surface scanning system and daily cone beam CT (CBCT). Additionally, a comparison of radiation treatment times will be performed, to ensure time-efficiency of CPAP-assisted RT. Finally, a cost-analysis will be set up.

Additionally, we aim to compare normal tissue complication probabilities (NTCP) for cardiac toxicities between standard radiation therapy and CPAP-assisted radiation therapy, using NTCP models from Darby et al. and those developed in study s685087[7]. These models incorporate dosimetrical data and clinical variables to predict a patient's risk of developing cardiac toxicity. The ultimate goal is not only to compare the dosimetrical differences between the two approaches, but also to assess their clinical significance by estimating the actual reduction in cardiac toxicity risk.

In summary, we expect a reduction in cardiac and/or pulmonal radiation doses in CPAP-assisted RT compared to standard RT (without CPAP), potentially also leading to a decrease in long-term radiation-induced cardiotoxicity (and or pulmonal toxicity). Additionally, this study may offer preliminary evidence suggesting CPAP as a viable alternative to DIBH for patients unable to perform DIBH. We also aim to develop a patient selection model based on laterality and extent of the irradiation field for identifying those who would benefit the most from CPAP-assisted RT. Furthermore, this research will assess clinical performance of CPAP-assisted RT in daily practice and provide guidelines for its clinical implementation in BC RT, encompassing considerations of accuracy, reproducibility, efficacy and cost-analysis. Additionally, patient compliance will be reported.

2 Objectives and Design

2.1 Study objectives and hypotheses

The study hypothesizes that using a CPAP device during RT for BC patients will decrease cardiac (and or pulmonal) radiation doses compared to standard RT (without CPAP-assistance).
The primary objectives is thus to demonstrate a decrease of approximately 0.5 Gy MHD by using CPAP-assisted RT compared to standard RT (without CPAP) in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):.
The secondary objectives include:

- To compare target volume coverage between standard and CPAP-assisted RT in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):
- To determine which patients benefit the most from CPAP-assisted RT by comparing dosimetric parameters on different OARs in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):
    - Whole heart
    - Cardiac substructures (large vessels, atria, ventricles, valves, conduction nodes, coronary arteries, coronary artery calcifications, heart base)
    - Lungs
    - Ipsilateral lung
    - Contralateral breast
    - Liver
    -
- To determine patient comfort and tolerance of CPAP-assisted RT by analysing patient questionnaires
- To compare reproducibility and accuracy between standard and CPAP-assisted RT by using surface scanning parameters and daily CBCT information.
- To compare DIBH performance between standard and CPAP-assisted RT by using surface scanning parameters and daily CBCT information.
- To compare time-effectiveness between standard and CPAP-assisted RT
    - Set-up time
    - Matching time
    - Radiation time
- To compare cost-analysis between standard and CPAP-assisted RT
- To compare normal tissue complication probabilities (NTCP) from various NTCP models (Darby et al. and models developed in study s68508) between standard and CPAP-assisted RT

2.2 Primary Endpoints

Difference in MHD in Gy between standard RT (without CPAP) and CPAP-assisted RT in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)):

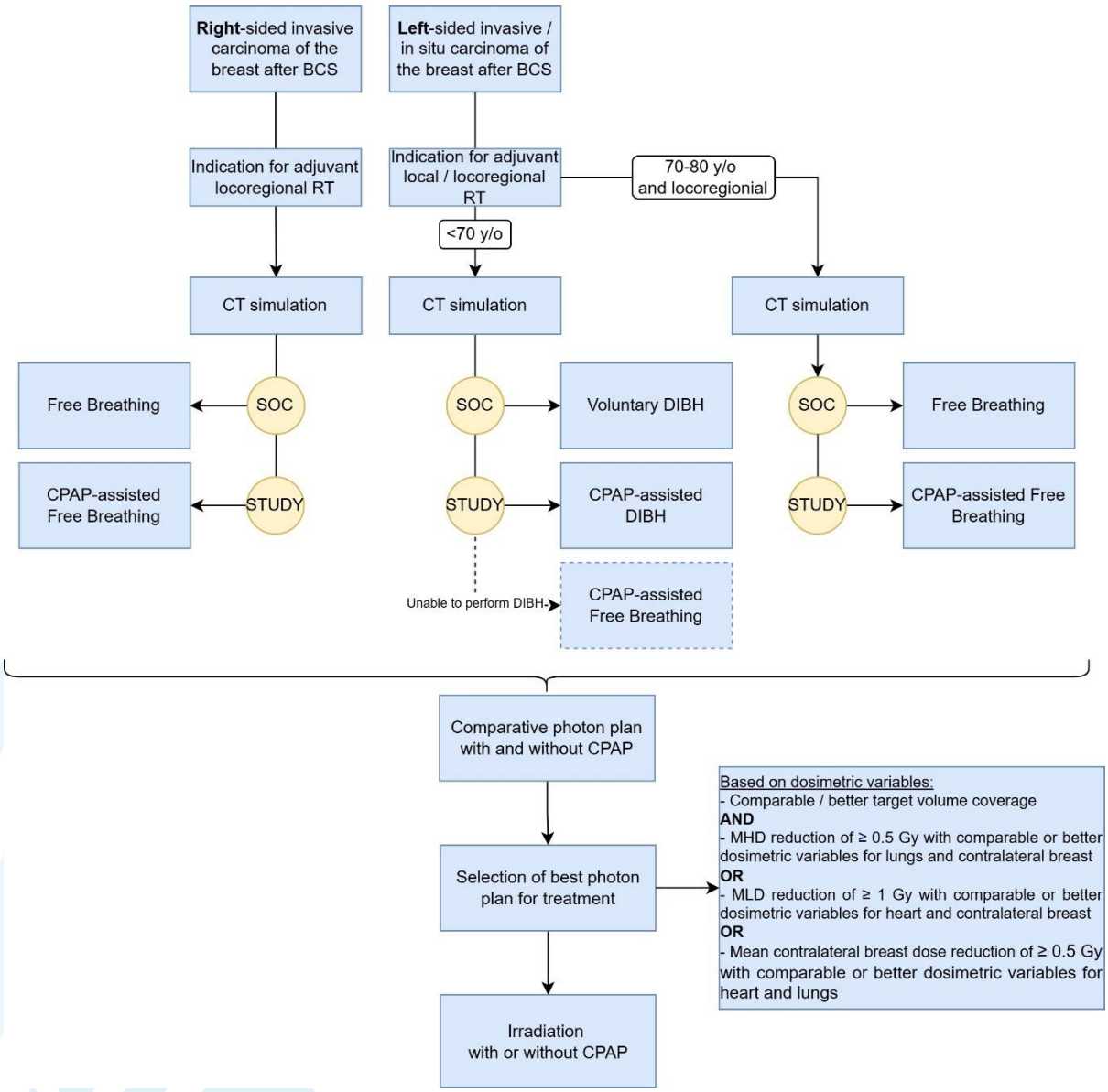
2.3 Secondary Endpoints

- Differences in target volume coverage between standard and CPAP-assisted RT
- Differences in cardiac dosimetry (whole heart and cardiac substructures) + other OAR dosimetry (lungs, ipsilateral lung, contralateral breast, liver) between standard and CPAP-assisted RT
- Likert scale scores from patient questionnaires
- Difference in mean deviation of surface, OAR and target volume positions per fraction (in mm) in standard vs CPAP-assisted RT (encompasses reproducibility: day-to-day variation in surface, OAR and target volume position)

- Difference in average surface, OAR and target volume maximum shift observed during each fraction (in mm) in standard RT vs CPAP-assisted RT (encompasses accuracy: difference of daily surface, OAR and target volume treatment position versus planning position)
- Difference in RT duration between standard and CPAP-assisted RT (minutes)
    - Set-up time
    - Matching time
    - Radiation time
- Difference in DIBH duration between standard and CPAP-assisted RT (seconds)
- Difference in total treatment costs between standard and CPAP-assisted RT (euro)
- Difference in normal tissue complication probabilities (NTCP) from various NTCP models (Darby et al. and models developed in study s68508) between standard and CPAP-assisted RT

2.4 Design of the Clinical Investigation

Prospective Non-Randomized Clinical Trial



2.5 Justification for the design of the Investigation

Previously published results have shown dosimetric benefits of the use of CPAP in RT for BC and other thoracic malignancies. A small retrospective study investigated the use of a CPAP device in combination with DIBH in left-sided BC patients showing clear dosimetric advantages on cardiac radiation doses [44]. Additionally, some small retrospective and non-randomized prospective studies also showed decreased cardiac doses when CPAP was used in a free breathing (FB) setting, for example in patients not able to perform DIBH [45–49]. The same CPAP-assisted strategy has been investigated in RT for other thoracic malignancies showing similar results confirming larger lung volumes and some also demonstrating decreased cardiac doses with CPAP [50–52]. One study in lung cancer patients did not show a dosimetric benefit on the heart, probably because of the use of a relatively low airway pressure and a nose mask instead of a nose and mouth mask [53].
In summary, preliminary evidence indicating potential advantages in RT dosimetry when using CPAP in BC RT exists. However, the evidence is limited by small sample sizes and/or the retrospective nature of most previous studies. To address this limitation, the primary objective of this study is to prospectively examine the impact of CPAP in optimizing RT in a large BC cohort to enhance the robustness of these findings. Moreover, to determine which patients benefit the most from CPAP-assisted RT we will compare dosimetric parameters in 4 cohorts of BC patients (right-sided, left-sided without RNI, left-sided with RNI(<70y/o) and left-sided with RNI (70-80 years old)). The rationale behind this is twofold. Firstly, the anatomical left-sided position of the heart, suggests a potential for more significant cardiac benefits from CPAP-assisted RT in left-sided BC patients. Secondly, patients undergoing irradiation of the RNI, including the internal mammary and subclavian glandular chain, may experience increased advantages with CPAP-assisted RT due to the otherwise close proximity of the RT target volume to multiple OARs. Due to these two factors, right-sided BC patients only requiring local breast RT (without RNI) will not be included in this study, because the presumed benefit of CPAP-assisted RT is too small.
Furthermore, we will also assess clinical performance of CPAP-assisted RT in daily practice and provide guidelines for its clinical implementation in BC RT, encompassing considerations of accuracy, reproducibility, efficacy and cost-analysis.

2.6 Expected Duration of the Investigation

The study duration for a single patient aligns with the standard radiation treatment course for BC, commencing with a CT simulation scan, typically followed by the initiation of RT approximately 2 weeks thereafter. The complete course consists of 15 radiation treatment fractions, administered at a frequency of 4 to 5 sessions per week, resulting in an average duration of slightly less than 4 weeks for the entire RT process. If a boost dose to the tumor bed is administered, this will be given in a simulteaneous way (integrated in the radiation of the breast/regional lymph nodes). No study-specific follow-up is provided after termination of RT.

Anticipated enrolment of patients is expected to take 1 year, followed by an additional year allocated for data analysis and subsequent publication of the results. Consequently, the anticipated timeframe for the study's completion is two years.

The end of the Investigation is defined as Last Patient Last Visit (LPLV). The CI shall notify the end of the Investigation to the EC within 15 days. The CI will submit a final report with the results of the Investigation, including any publications/abstracts, within one year of the end of the clinical investigation or within three months in case of an early termination. In absence of EUDAMED, the Clinical Investigation Report (CIR) shall be submitted to the involved EC.

The Sponsor, EC or authorized regulatory authority can decide to halt or prematurely terminate the Investigation when new information becomes available whereby the rights, safety and well-being of participants can no longer be assured, when the integrity of the Investigation has been compromised, or when the scientific value of the Investigation becomes obsolete and/or unjustifiable. In case the Sponsor decides to temporary halt or prematurely end the Investigation, or to close a Participating Site in case of major non-compliance and/or critical safety issues, the Sponsor will notify the concerned EC within 15 days

of early termination or temporary halt, providing a justification of the event. In the event that the sponsor has temporarily halted or early terminated the Investigation on safety grounds, the Sponsor will inform the EC within 24 hours of the event. In absence of EUDAMED, local guidelines with regards to notifications and submissions to the concerned EC will be followed.

Circumstances requiring premature treatment interruption or discontinuation of the Investigation, include but are not limited to:

- Safety concerns related to IMD or unacceptable intolerability

3 Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Investigation have to meet **all** of the following criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures
2. At least 40 years of age and 80 years or younger at the time of signing the Informed Consent Form (ICF)
3. Female patients
4. Patients that underwent breast conserving surgery (BCS)
5. Left-sided invasive BC / in situ carcinoma with indication for adjuvant RT (<70 years old)
6. Left-sided invasive BC with indication for adjuvant locoregional RT (including RT of the regional lymph nodes) (70-80 years old)
7. Right-sided invasive BC with indication for adjuvant locoregional RT (including RT of the regional lymph nodes)
8. Prior chemotherapy allowed
9. Prior immunotherapy allowed
10. Prior / concomitant hormonal therapy allowed
11. Prior / concomitant HER2-targeted therapy allowed

All participants that are considered for Investigation participation per the above criteria, will be documented via applicable log forms in Investigator Site File (including Screen Failures).

3.2 Exclusion criteria

Participants eligible for this Investigation must **not** meet any of the following criteria:

1. Patient has active bullous lung disease, bypassed upper airway, pneumothorax, cerebral spinal fluid leaks, abnormalities of the cribriform plate (contra-indications for the use of CPAP)
2. Patient has history of major head trauma and/or pneumocephalus (contra-indications for the use of CPAP)
3. Any disorder, which in the investigator's opinion might jeopardise participant's safety or compliance with the CIP.
4. Female who is pregnant, breast-feeding or intends to become pregnant (which is a contra-indication for RT in general)
5. Male BC patients
6. Patients that underwent mastectomy Patients whose initial tumor was located just beneath the skin (defined as being less than 28mm below the breast surface), indicating the need for an electron boost
7. Patients requiring RT boost on positive lymph nodes
8. Distant metastasis
9. Breast implants in situ
10. Right-sided in situ carcinoma

11. Right-sided invasive BC only requiring local adjuvant RT (without irradiation of the regional lymph nodes, because the presumed benefit on cardiac doses of local right-sided breast irradiation is assumed to be rather small because of the left anatomical position of the heart)
12. Bilateral BC
13. Concomitant use of chemotherapy during RT
14. Substantial comorbidities, incompatible with RT or CPAP use, estimated by the treating radiation oncologist
15. Insufficient arm mobility to perform comfortable arm positioning in radiation treatment position, evaluated by the treating radiation oncologist
16. Other active oncological disease / treatment with the exception of non-melanoma skin cancer
17. Previous RT with overlapping RT fields with actual target volume

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled/randomized in the Trial and will be identified via applicable log forms in Investigator Site File.

4 Study Procedures

4.1 Selection of Participants / Recruitment

Potential participants will be identified and recruited during patient consultations in one of the participating sites. No additional recruitment material (such as for example flyers, social media advertising, audio/video recordings) will be used.

4.2 Investigation assessments and procedures

Trial procedures and their timing are summarized in the Study Flowchart.

4.2.1 Participant consent and withdrawal of consent

The Investigation will be conducted only on the basis of prior informed consent by the participants and/or their legally authorized representative(s). As such, no Investigation-related procedures will be conducted prior to obtaining written informed consent from potential participants.

The process for obtaining and documenting initial and continued informed consent from potential participants will be conducted in accordance with ISO 14155:2020, applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the ISF at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the CIP section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Investigation for any reason at any time. The participant's request to withdraw from the Investigation must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Study data and samples collected before withdrawal can be used in the study. No new study data or samples will be collected after withdrawal of the participant.

4.2.2 Randomization Procedure (if applicable)

Not Applicable

4.2.3 Other Investigation assessments and procedures

Additional information to the anticipated investigations taking place within this study:

Consultation:

The treating physician will meet the patient to discuss side effects and other concerns about the condition and treatment. A consultation may be accompanied by a (focused) clinical examination.

CT scan:

A CT simulation scan is used to plan and optimize radiation treatment.

Patient-reported questionnaires:

During and after treatment, we will ask patients to answer some questions regarding side effects and quality of life by using validated questionnaires.

4.3 Premature discontinuation

Participants may voluntarily discontinue from the Investigation treatment and/or prematurely end their participation in the Investigation for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g., via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Investigation, to temporarily interrupt or permanently discontinue the treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Circumstances requiring premature treatment interruption or discontinuation of the Investigation, include but are not limited to:

- Investigation participation while in violation of the inclusion and/or exclusion criteria
- Pregnancy
- Intention of becoming pregnant
- < Safety concerns related to IMD or unacceptable intolerability>

In any such case of early termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up. It is recommended that follow-up information will be collected as follows:

If a patient withdraws from the study while undergoing RT, we will highlight the crucial medical importance of finishing the radiation course for effective oncological disease control and provide the opportunity to resume the radiation treatment according to standard of care as soon as possible.

Since no study-specific follow-up is provided after termination of RT, participant discontinuation of the study after completing RT does not affect study protocol, hence no different follow-up is provided in this case.

For participants whose status is unclear because they fail to appear for visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Investigation (e.g., dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

5 Investigational Medical Device (IMD)

Investigational Medical Device Name (& company brand)	**CE mark (Y – N - NA)**	**Used within Indication (Y or N)**	**Manufacturer of the device**
Philips Respironics DreamStation I	Y	Y	Philips
F&P Evora™ Full Face mask	Y	Y	Fisher & Paykel Healthcare

5.1 Intended use

The Philips Respironics DreamStation system delivers positive airway pressure therapy in spontaneously breathing patients weighing over 30 kg. It is developed for use at home or in a hospital/institutional environment. It is most commonly used for the treatment of Obstructive Sleep Apnea Syndrome (OSAS) (https://www.documents.philips.com/doclib/enc/11405972/DreamStation_CPAP_User_Manual.pdf).

5.2 Identification and description of the IMD

The Philips Respironics DreamStation system delivers positive airway pressure therapy in spontaneously breathing patients weighing over 30 kg. It is developed for use at home or in a hospital/institutional environment. It is most commonly used for the treatment of Obstructive Sleep Apnea Syndrome (OSAS) (https://www.documents.philips.com/doclib/enc/11405972/DreamStation_CPAP_User_Manual.pdf). It will be used in combination with The F&P Evora™ Full Face mask. This device is intended to be used by adults weighing ≥ 30 kg who have been prescribed non-invasive positive airway pressure therapy such as CPAP (https://resources.fphcare.com/content/ui-618441.pdf) .
In our study, this DreamStation 1 CPAP device will be used to provide positive airway pressure, in order to assist and enhance spontaneous breathing and DIBH during RT for BC patients. It will be used in combination with a F&P Evora Full compact full-face PAP mask to cover both nose and mouth.
Patients will be educated about the use of the CPAP device and mask in a coaching session of 30 minutes, prior to CT simulation. As a first step, the patient will be educated about the use of the system by our RT nurse or the treating RT physician. Next, fitting of the full-face mask is provided, since correct fitting is very important to prevent leakage of pressure. Subsequently, the patient will be connected to the CPAP device, and the airway pressure will be gradually elevated from 7 cmH20 to 15 cmH20 over a ten-minute interval to acclimate to breathing with the device. Throughout this duration, the patient will have the opportunity to communicate whether the final pressure of 15 cmH20 is both comfortable and sustainable. Once the patient has adequately adapted to breathing with the device, the commencement of the effective preparation for RT will start, while continuing breathing with the CPAP device.

5.3 Device Accountability

For both the Philips Respironics DreamStation 1 and the F&P Evora™ Full Face mask preparation is not applicable. 5 DreamStation 1 study devices will be available for the duration of the entire study. All of these will be labelled as followed:

- "DreamStation1_Philips_RT_Sim1" (this device will be stored at CT simulation 1 UZ Leuven)
- "DreamStation1_Philips_RT_Toestel1" (this device will be stored at LINAC 1 UZ Leuven)
- "DreamStation1_Philips_RT_Toestel2" (this device will be stored at LINAC 2 UZ Leuven)
- "DreamstationI_Philips_RT_Toestel3" (this device will be stored at LINAC 3 UZ Leuven)
- "DreamStation1_Philips_RT_Reserve" (this device will serve as a spare device in the event of defects in other devices, ensuring that the repair of one device does not disrupt the workflow of the study. This device will be stored at CT simulation 1 UZ Leuven)

The devices should be stored at room temperature, away from any heating or cooling equipment. Sterilization of the devices is unnecessary; thorough cleaning with a Trionic wipe after each use is deemed sufficient.

For every individual patient randomized to the investigational arm an individual F&P Evora™ Full Face mask and connecting tube will be purchased with study budget of the available funding. The mask and tube will be used by a single patient during the entire radiation treatment and will be stored at the radiation treatment console, labelled as followed: "Mask_PatientSurname_PatientDateOfBirth". After completion of the entire radiation treatment all masks and tubes will be collected together and will be stored at CT simulation 1 of UZ Leuven until completion of the study.

6 Safety reporting

6.1 Definitions

The definitions and reporting requirements adopted in this CIP are based on the MDR, ISO 14155:2020 and the MDCG 2020-10/1 European guideline and the vigilance provisions.

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

Note:
a. This definition includes events related that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

6.1.2 Serious Adverse Event (SAE)

A SAE is any adverse event that led to any of the following:

a) death,
b) serious deterioration in health of the subject, that resulted in any of the following:
   - life-threatening illness or injury,
   - permanent impairment of a body structure or a body function,
   - hospitalisation or prolongation of patient hospitalisation,
   - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
   - chronic disease,
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

6.1.3 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device or a comparator.

6.1.4 Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

An Unanticipated Serious Adverse Device Effect is any SADE of which the nature, severity or outcome is not consistent with the reference safety information.

6.1.5 Device Deficiency (DD)

A DD is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

6.1.6 Adverse Events of Special Interest (AESI)

The following events should be reported within the same timelines as SAEs:

- Not Applicable

6.2 Adverse Events that do not require reporting

In general, the following should <u>not be reported as AEs:</u>

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness, unless the pre-existing condition appears to be worsened).

- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first investigation-related activity after the subject has signed the informed consent.

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the investigation:

- Radiation-induced erythema/epidermolysis/oedema of the irradiated skin
- Radiation-induced oesophagitis
- Radiation-induced fatigue

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

6.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE form, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE forms.

The following minimum information should be recorded for each AE:

- AE description

- start and stop date of the AE

- severity

- seriousness

- causality assessment to the Investigational Medical Device (IMD) and/or study procedures

- outcome

6.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.

- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**

Not related	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.
Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal relationship	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that • the investigational device or procedures are applied to; • the investigational device or procedures have an effect on; - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); - other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

6.3.2 Timelines for reporting

- After informed consent has been obtained but prior to first use of the IMD, only adverse events caused by a study specific procedure should be reported

- After first use of the IMD, adverse events will be reported as follows:
    - All AEs and SAEs related to a study procedure or the IMD, AESIs and Device Deficiencies will be reported until last (follow-up) visit.

All SAEs and AESI as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

SAE details will be reported by the Investigator to the sponsor:

- By completing the SAE form in the (e)CRF

If an authorised Investigator from the reporting site is unavailable, initial reports without causality assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

6.3.3 Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and/or until all related queries have been resolved.

SAEs after the end of the investigation: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMD or experiment after the subject has ended the investigation, the Investigator should report this SAE within the same timelines as for SAEs during the investigation.

6.3.4 Death

All deaths will be reported without delay to the sponsor (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). If considered a reportable event, the sponsor must notify the EC(s) and CA(s) for materiovigilance as soon as possible after becoming aware.

6.4 Recording and reporting of Device Deficiencies

Each Device Deficiency must be documented by the Investigator in the source documents and reported to the Sponsor on a Device Deficiency form.

If the Device Deficiency leads to the occurrence of a (S)ADE, the (S)ADE must also be reported by the Investigator to the Sponsor on the appropriate forms and within the specified timelines.

6.5 Reporting requirements to Ethics Committees (EC's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs, AESIs and Device Deficiencies against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable EC's based on applicable legislation.

6.5.1 Sponsor's reporting of Serious Adverse Events and Device Deficiencies

The Sponsor is responsible to report to the EC's where the clinical investigation has commenced:

- Any SAE that has a **causal** relationship with the device, the comparator or the investigation procedure* or where such causal relationship is reasonably possible;
- Any Device Deficiency that might have led to a SAE if:
    a) Appropriate action had not been taken or,
    b) Intervention had not occurred or,
    c) If circumstances had been less fortunate
- New findings/update in relation to already reported reportable events.

**a study-specific procedure related to the use of the investigational device or comparator (outside the standard of care).*

These 'reportable events' must be reported within the following timelines:

- A reportable event which results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it must be reported immediately, but not later than **2 calendar days** after awareness by the sponsor of a new reportable event or of new information in relation with an already reported event.
- Any other reportable event or a new finding/update to it must be reported immediately, but not later than **7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

6.6 Sponsor's reporting of Materiovigilance to Competent Authorities (CA's)

Serious incidents or potential serious incidents related to the use of a CE marked device used within its intended purpose should be reported to the CA according to the materiovigilance provisions.

The following should be notified as soon as possible:

- Any dysfunction or any change of the characteristics and/or performance of a device, and any inadequacy in the labelling or instructions, which might lead to or have led to death or serious relapse in the state of health of a patient, a user or a third party.
- Any incident that might have resulted in one of the following clinical implications:
    • death
    • life-threatening injury
    • permanent or significant impairment of a body structure or a body function
    • hospitalisation or prolongation of patient hospitalization
    • need for medical or surgical intervention
    • congenital physical or mental impairment, foetal distress or foetal death
    • delayed or incorrect diagnosis or treatment
    • transfusion of improper materials

This also includes any risk of a serious incident that could be prevented by the actions and interventions of the involved persons.

6.7 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	as defined in CIP
	SAE	SAE form	sponsor	asap, but no later than 3 calendar days after awareness
	Device Deficiency (DD)	DD form + AE/SAE form (if applicable)	sponsor	as defined in CIP (exception: within 3 calendar days if considered reportable event)
	death	SAE form	sponsor	asap
Sponsor	all reportable events (of all participating sites)	EU SAE report form (excel)[1]	- Ethics Committee(s)	asap, but no later than - 2 calendar days (in case of risk of death or serious injury/illness that requires prompt remedial action for other patients, users or other persons) - 7 calendar days (all other reportable events)
	Materiovigilance	Meddev report form[2]	- CA for Belgium -> FAGG: via mail to vigilance.meddev@fagg-afmps.be	asap

[1]The SAE report form in excel format can be downloaded from the following web page: https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

[2]The Meddev report form can be downloaded form the following web page: https://www.fagg.be/sites/default/files/content/notification_incident_nl_0.pdf

6.8 Data Safety Monitoring Board (DSMB)

After a thorough evaluation of the potential risks to Investigation participants and considering the nature, design and complexity of the clinical Investigation, the Sponsor has determined not to establish a DSMB. This decision is grounded in our conclusion that this is a low risk clinical Investigation in which the IMD has a CE mark and is used within indication. In addition, the potential risks associated to the study procedures and protocol design are comparable to that of standard medical care.

The Investigation is committed to ensuring the safety and well-being of all participants at all times by adhering to the latest version of ISO 14155:2020 and other relevant and applicable standards and legislations.

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the study-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical study report.

7.1 Sample Size Determination

Approximately 83 participants will be screened to achieve an estimated total of 73 evaluable participants.

7.2 Statistical Analysis

<SAMPLE SIZE

Our aim is to evaluate whether CPAP-assisted radiation treatment improves cardiac radiation doses in 3 cohorts of BC patients (right-sided BC, left-sided BC without RNI, left-sided BC with RNI). A decrease of 0.5 Gy Mean Heart Dose (MHD) by using CPAP-assisted RT compared to a standard protocol was deemed clinically relevant. Retrospective data provided the following information on means and standard deviation (SD) of MHD in the first 3 cohorts: right-sided BC Mean MHD 1.03, SD 0.52; left-sided BC without RNI Mean MHD 1.15, SD 0.71, left-sided BC with RNI Mean MHD 2.29, SD 0.82. No information was available on the correlation between paired measurement of MHD with and without CPAP. A correlation of 0.5 was assumed for the sample size calculation, leading to sample sizes of 11 (right-sided BC), 18 (left-sided BC without RNI), and 24 (left-sided BC with RNI) patients, or 53 patients in total. The sample size calculation was performed assuming a two-sided paired t-test, adopting a 5% test-wise significance level, and 80% of power. To account for the uncertainty on the assumed correlation between paired measurements, a blinded sample size recalculation will be performed after inclusion of approximately 50% of the patients. The correlation between paired measurements will be calculated and the sample size will be re-estimated with the observed correlation. In case the correlation turns out lower than previously anticipated, the sample size will be increased. For the additional subgroup of 70- to 80-year-old patients with left-sided breast cancer and an indication for RNI, no baseline data on MHD were available. Therefore, we estimate to include approximately 20 patients in this group, extrapolated from the sample sizes used for the other subgroups. Since a sample size recalculation is planned, a specific calculation for this subgroup will also be performed at that time. In conclusion, with the inclusion of this final group, we anticipate a total sample size of approximately 73 patients.

STATISTICAL ANALYSIS

Descriptive statistics on the sample will be provided presenting categorical variables by frequencies and percentages, and continuous variables by mean with standard deviation, median and quartiles. >

7.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	For each of the three cohorts, the following analysis is planned: A two-sided paired t-test will be performed to compare the difference in MHD between the standard protocol and CPAP. The mean difference will be estimated with 95% confidence interval. A 5% significance level will be adopted for the analysis in each of the 4 cohorts.
Secondary	The comparison between standard protocol and CPAP with regards to dosimetric outcomes for different organs at risk (OAR) will be analyzed in analogy with the primary outcome analysis. Patient comfort and tolerance of CPAP-assisted RT by assessed by patient questionnaires will be analyzed descriptively. A Bland-Altman analysis will be performed to analyze agreement of surface scanning parameters obtained with CPAP or standard protocol. DIBH performance, time effectiveness, cost analysis and NTCP differences will be compared between standard and CPAP-assisted RT for left-sided BC on surface scanning and CBCT parameters using the same approach as the primary outcome analysis. The focus of the secondary analyses will be on the estimation of effect sizes with 95% confidence intervals. Formal tests performed will adopt a 5% significance level, nevertheless p-values will be interpreted carefully, recognizing the risk inflated type I error rate. Conclusions will be drawn as hypothesis-generating. We expect negligible missing observations as almost all outcome measurements are taken at Visit 2 and collected by clinical staff.
Exploratory	Not applicable

7.2.2 Other Analysis

Not applicable

7.3 Interim Analysis and Final Database Lock

Not applicable

8 Data handling

Redcap will be used to capture study related data. Data will be stored on KULeuven/UZ Leuven hardware and servers, thus protected by its firewalls. The patient data will be coded. There will be a coding file using a study number with the matched EAD number. This coding file will only be accessible by Prof. Weltens (principle investigator), Prof. Van Aelst, Prof. Lambrecht, dr. Aline Van der Vorst and dr. Johanna Jacobs (co-investigators).

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Investigation will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source data will be collected and recorded in the participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Investigation).

It remains the responsibility of the Investigator to check that all data relating to the Investigation, as specified in the CIP, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

Redcap will be used as eCRF to capture study related data.

(e)CRFs are provided by the Sponsor for each participant. The Investigation data will be transcribed from the source records (i.e., participant's medical file or study-specific source data worksheets) into an (e)CRF by study staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The following data will be collected in the (e)CRF :

- Patient characteristics: sex, date of birth, age, weight, length
- Medical history
- Cardiovascular risk factors
- Oncological data
    - Tumour laterality: left / right breast
    - Tumour Stage: clinical and pathological Tumor-Node-Metastasis (TNM)
    - Date of cancer diagnosis
    - Pathological characteristics: tumour size, nodal status, histological subtype, histological grade, hormone and HER2 receptor positivity, Ki67
    - Surgical therapy
        - Type of surgery
            - BCS
            - Sentinel node procedure
            - Axillary dissection
    - Systemic therapy
        - Chemotherapy regimen: scheme, setting neoadjuvant/adjuvant, start therapy, cycles planned, cycles received, dose used
        - Her2-directed regimen: setting neoadjuvant/adjuvant, start therapy, cycles planned, cycles received, dose used
        - Hormonal therapy: setting neoadjuvant/adjuvant, start therapy, cycles planned, cycles received, dose used

        - Immunotherapy: setting neoadjuvant/adjuvant, start therapy, cycles planned, cycles received, dose used
    - Radiation therapy
        - Radiation field
            - Breast
            - Regional lymph nodes (level I, II, III, IV, rotter, internal mammary nodes)
        - Radiation dose
            - Total dose
            - Dose per fraction
            - Target volume coverage
            - Dosimetry parameters of different OAR
                - Whole heart
                - Cardiac Substructures
                - Lungs
                - Ipsilateral lung
                - Contralateral breast
                - Liver
                -
        - Administration of a boost to the tumour bed
            - Total dose
            - Dose per fraction
            - Location of boost: inner/outer, upper/lower quadrant
        - Application of DIBH technique: yes or no
        - Application of CPAP-assisted RT: yes or no
        - Radiation technique: 3D conformal radiotherapy, IMRT, VMAT, PT, combination
    - If applicable, date and cause of death
        - Oncological
        - Cardiovascular
        - Infectious
        - Other
        - Unknown
- Differences in normal tissue complication probabilities (NTCP) from various NTCP models (Darby et al. and models developed in study s68508) between standard and CPAP-assisted RT
-

We expect negligible missing observations as almost all outcome measurements are known at Visit 2 and collected by clinical staff.

8.1.1.2 Data Validation

All data relating to the Investigation must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized study staff.

Proper audit trails must be available to demonstrate the validity of the Investigation data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e., who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Study Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A DMP will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the DSMB.

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the study-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Investigation must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the GDPR, and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Study staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Investigation disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Investigation as described in this CIP. The collection, processing and disclosure of personal data, such as participant health and medical information, is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each participant, and will maintain a TMF/ISF containing all study documents, as specified in ISO 14155:2020 Annex E entitled "*Essential clinical investigation documents",* and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the GDPR).

8.2 Audits and Inspections

The Investigator will permit direct access to study data and documents for the purpose of monitoring, audits and/or inspections by authorized entities, such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such, (e)CRFs, source records and other study related documentation (e.g., ISF, TMF, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

In accordance with ISO 14155:2020, the Sponsor is responsible for monitoring the Investigation to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the study procedures have been followed as shown in the approved CIP, and that relevant study data have been collected and reported in a manner that assures data integrity.

UZ Leuven Clinical Trial Center (CTC) performs a risk analysis to determine the monitoring strategy. Based on this risk assessment, the clinical trial was classified as 'low risk' as the potential risks associated to study procedures and protocol design are comparable to that of standard medical care since the IMD has a CE label and is used within indication.

Based on the above risk assessment and as permitted by GCP, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by GCP) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data. Nonetheless, the UZ Leuven study team will take all possible measures to assure the quality and integrity of trial data and to safeguard the safety and wellbeing of trial participants, in accordance with the requirements set out in GCP and ISO:14155.

8.4 Archiving

As specified in ISO 14155:2020 section 8.6, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Clinical Investigation Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Investigation.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Investigation.

The Sponsor and Investigator is responsible for archiving study specific documentation (such as but not limited to the CIP, any amendments thereto, the final Clinical Investigation Report (CIR) and the study database), according to ISO 14155:2020. Source data and site-specific study documents (such as but not limited to the original signed ICFs) will be archived by the Participating Site(s) according to local practice, and for a period of at least 10 years after the clinical Investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.[1] Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

9 Ethical and Regulatory Considerations

9.1 Ethics Committee (EC) review & reports

Before the start of the Investigation, this CIP and other related documents (e.g., ICF, advertisements, IB, etc.) will be submitted for review to the EC for authorization. The Investigation shall not commence until such approval have been obtained and until other relevant essential Investigation documents, such as duly signed contract agreements, evidence of adequate financing etc. are in place..

9.2 Peer review

This CIP was peer reviewed by 3 independent experts. Peer review was conducted by expert referees to the professional and scientific standards expected for clinical studies.

9.3 Regulatory Compliance

The Investigation will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical investigations in the EU, as provided for in the MDR, as applicable, and any subsequent amendments, as well as in compliance with ISO 14155:2020, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th, 2004 regarding experiments on the human person (as amended), or the Belgian law of December 22nd, 2020 concerning medical devices, as applicable, the Belgian royal decree of May 18th, 2021 concerning clinical investigations of medical devices, and with the GDPR, the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd, 2002 on patient rights, and all other applicable legal and regulatory requirements.

9.4 CIP / GCP compliance

The Investigation must be performed in accordance with the CIP, ISO 14155:2020, and applicable regulatory and country-specific requirements. ISO 14155:2020 is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical investigations that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety and well-being of participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible, reliable and reproducible.

The Investigator and study team acknowledge and agree that prospective, planned deviations or waivers to the CIP are not permitted under applicable regulations on clinical investigations. However, should there be

[1] According to UZ Leuven policy, Study documents will be archived for at least 25 years following termination of Investigation.

an accidental CIP- deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Investigation. Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a major protocol deviation.

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Investigation, even if this action represents a deviation from the CIP. In such cases, the Sponsor should be notified of this action and the EC should be informed according to local procedures and regulations.

The Sponsor has performed a risk assessment to reduce anticipated risks with regards to the safety, wellbeing and rights of the participants as well as with regards to the reliability and robustness of the clinical Trial data.

9.5 Data protection and participant confidentiality

The Investigation will be conducted in compliance with the requirements of the GDPR, the relevant Belgian laws implementing the GDPR, including the Belgian Privacy Act of July 30th, 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Sponsor, Participating Site and the Investigator shall have and maintain in full force and effect during the term of this Investigation, and for a reasonable period following termination of the Investigation, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Article 32 of the Belgian Law concerning medical devices dated December 22nd, 2020 applies. Prior to the start of the Investigation, the Sponsor shall enter into an insurance contract in order to adequately cover participants from Belgian Participating Sites in accordance with Article 32 of the said law.

For non-Belgian Participating Sites

The Participating Site shall have and maintain in full force and effect during the term of this Investigation (and for a reasonable period following termination of the Investigation), adequate insurance coverage for other possible damages resulting from the Investigation at the Participating Site, as required by local law. Each such insurance coverage shall be in amounts appropriate to the conduct of the services of the Participating Site under this Investigation. The Participating Site and Sponsor shall be solely responsible for any deductible or self-insured retention under any such policies.

9.7 Amendments

As specified in ISO 14155:2020 section 7.5.1, amendments must not be implemented prior to EC review and/or approval, as applicable. Under emergency circumstances, deviations from the CIP to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to EC as soon as possible.

In accordance with the Belgian law of December 22nd, 2020 concerning medical devices, the Sponsor may develop a non-substantial amendment at any time during the Investigation. If a substantial amendment is introduced to the CIP, or the documents that supported the original application for the clinical Investigation, authorisation is needed, the Sponsor must submit a valid substantial amendment for approval to the EC. The EC will provide a response in accordance with timelines defined by applicable law. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial. In absence of EUDAMED, local guidelines with regards to notifications and submissions to the concerned EC will be followed.

Amendments to the Investigation are regarded as 'substantial' when they are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

9.8 Post-Study activities

After completing the study, the acquired data will undergo initial analysis and subsequent publication. If this study confirms the anticipated advantages of CPAP-assisted RT, validation through larger-scale studies in independent RT centres is suggested before its integration into standard of care. Meanwhile, BC patients will retain access to current standard of care RT treatment.

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (most recent version) and European and Belgian regulations require that every research involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Study.

In addition, the CI will fulfil its ethical obligation to disseminate and make the research results publicly available. As such, the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors, and in accordance with the requirements of the respective medical journal.

For multicentre Investigations, it is anticipated that the primary results of the overall Investigation shall be published in a multicentre publication.

Participating Sites are not allowed to publish any subset data or results from the Investigation prior to such multicentre publication.

Any publication by a Participating Site must be submitted to the Sponsor for review at least 30 calendar days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to 3 months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Investigation or made in the performance of the CIP ("Inventions") shall vest in the Sponsor. If the Investigation is multicentric, the Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. The Sponsor and the Participating Site have expressly agreed that any and all study data as collected and prepared in the performance of the CIP shall be the sole property of the Sponsor, unless otherwise agreed in the Investigation agreement between the Sponsor and the Participating Site.

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Appendices

13 Appendix 1: Clinical Investigation Plan history

Original CTP version:	1.0 dated 11/04/2025

Amendment #1:	<1.3> dated 11/04/2025
Modifications made / Reason for amendment:	
Secondary endpoints	Addition of comparison of dosimetrical differences on cardiac substructures, as well as addition of comparison of normal tissue complication probabilities between standard and CPAP-assisted RT. Furthermore accuracy and reproducibility will be assessed in terms of surface, OAR and target volume changes on surface scannings and CBCT parameters.
In -and exclusion criteria	Post-mastectomy irradiation, electron boost delivery (for superficial tumor beds) and nodal boosts were excluded to improve comparability between groups and ensure a more homogeneous patient population.
Identification and description of the IMD	The positive airway pressure will be increased in two stages, rather than three, from 7 cmH2O to 15 cmH2O over 10 minutes, as the CPAP device can be programmed to automatically deliver this pressure adjustment. This approach minimizes the need for manual intervention by the nurses and ensures accurate implementation.
< CIP section reference>	<describe modifications made>

Amendment #2:	<CIP version number> dated 11/04/2025
Modifications made / Reason for amendment:	
Inclusion criteria	Broadening of the inclusion criteria from 50-70 years old to 40-70 years old
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>

Amendment #3:	<1.5> dated 11/04/2025

Modifications made / Reason for amendment:	
Inclusion criteria	Addition of a patient subgroup: 70-80 year old left-sided breast cancer patients with an indication of regional nodal irradiation
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>
< CIP section reference>	<describe modifications made>

14 Appendix 2: Patient Questionnaires

Tolerance of CPAP-assisted RT for **right-sided** patients

Likert scale	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1. The CPAP mask fits perfectly under my nose and mouth.					
2. The CPAP mask is straining too hard on my face.					
3. Wearing the CPAP mask is comfortable for me.					
4. The 15 minutes preparation before the simulation / irradiation are beneficial to get used to breathing with the mask.					
5. The speed at which the air pressure increases during the preparation is tolerable.					
6. In general, using the CPAP mask for breathing is well tolerated.					
7. With each use, breathing through the CPAP mask becomes progressively easier.					
8. The setup for each radiation session with the CPAP device proceeds smoothly.					

Tolerance of CPAP-assisted RT for **left-sided** patients

Likert scale	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
1. The CPAP mask fits perfectly under my nose and mouth.					
2. The CPAP mask is straining too hard on my face.					
3. Wearing the CPAP mask is comfortable for me.					
4. The 15 minutes preparation before the simulation / irradiation are beneficial to get used to breathing with the mask.					
5. The speed at which the air pressure increases during the preparation is tolerable.					
6. In general, using the CPAP mask for breathing is well tolerated.					
7. With each use, breathing through the CPAP mask becomes progressively easier.					
8. The setup for each radiation session with the CPAP device proceeds smoothly.					
9. Performing Deep Inspiration Breath Hold with the CPAP-mask is tolerable.					

15 Appendix 3: [Funding - Myny-Vanderpoorten Fonds and AIR LIQUIDE MEDICAL nv - VitalAire Grant]

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AIR LIQUIDE MEDICAL nv - VitalAire offered a Grant for acquisition of essential CPAP equipment solely.