GZA vzw

Clinical Protocol

Masks Against Surface-Scanning for radiation therapy immobilisation in head and neck cancer (MASSC study)

Study number:	CTOR20051GZA
Clinical Phase:	0
Protocol version and date:	Version 1.0.1; August 2021
EudraCT/BUN number:	/
Sponsor:	GasthuisZusters Antwerpen vzw Oosterveldlaan 22 2610 Wilrijk

This study will be conducted in compliance with the protocol, the current International Conference on Harmonization and the guidelines for Good Clinical Practices (ICH-GCP), the principles of the Declaration of Helsinki (version 2002) and any applicable regulatory requirements.

Confidentiality Statement

This document and its contents are the property of and confidential to GZA vzw. Any unauthorized copying or use of this document is prohibited.

SIGNATURE PAGE

Protocol title: “Masks Against Surface-Scanning for radiotherapy immobilisation in head and neck cancer.”

The signatory agrees to the content of the final clinical study protocol as presented.

Sponsor approval:

Signature: _____ Date: _____

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Investigator agreement

Protocol title: “Masks Against Surface-Scanning for radiotherapy immobilisation in head and neck cancer.”

I confirm that I have read this protocol, I understand it and I shall work according to this protocol and to the ethical principles stated in version of 2002 of the Declaration of Helsinki, the current International Conference on Harmonization (ICH) and the guidelines for good clinical practices (GCP) or the applicable laws and regulations of the country of the study site, for which I am responsible, whichever provides the greater protection of the individual.

I am aware of my responsibilities as an Investigator/Representative under the good clinical practices, national regulations and trial protocol. I agree to appropriately direct and assist the staff under my control, who will be involved in this clinical trial. This is documented in a training log.

Signature: _____ Date: _____

Name: _____

TABLE OF CONTENTS

Abbreviations

AE	Adverse Event
CBCT	Cone Beam Computed Tomography
CRF	Case Report Form
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EOS	End Of Study
GCP	Good Clinical Practice
HNC	Head and Neck Cancer
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PICO	Patient Intervention Comparison Outcome
RT	Radiotherapy
SAE	Serious Adverse Event
SS	Surface Scanning

STUDY SYNOPSIS

Protocol title:	Masks Against Surface-Scanning for radiation therapy immobilisation in head and neck cancer.
Alias:	MASSC study
Protocol number:	CTOR20051GZA
EudraCT/BUN number:	
Sponsor:	GZA vzw Oosterveldlaan 22, 2610 Wilrijk, Belgium
Principal Investigator:	Dr. Daan Nevens Iridium Kankernetwerk Phone: +32(0)3443, Fax: +32(0)3443 Daan.nevens@gza.be
Investigator(s)/study center(s):	GZA Sint-Augustinus
Study objectives and endpoints:	**Primary objective** To compare the accuracy and reproducibility of radiation therapy (RT) with open face masks and surface-scanning (SS), and with SS alone without masks to irradiation with a full thermoplastic mask, for patients with head and neck cancer. **Primary endpoint** Set-up and treatment accuracy, determined by *in-vivo dosimetry* using PerFRACTION, and by the evaluation of *intrafractional motion* by comparing a CBCT before and at the end of treatment in patients receiving RT with an open mask, without a mask and using a closed thermoplastic mask. **Secondary objectives** 1) to demonstrate that irradiation with open face masks and SS or no face masks and SS for patients with head and neck cancer reduces the *patients' levels of distress* when compared to irradiation with full thermoplastic masks. 2) to demonstrate that irradiation with open face masks and SS or no face masks and SS is *feasible for the treating RTT's*. **Secondary endpoints** 1) *Level of distress of patients,* determined by using the subjective units of distress scale (scale of 0-100). 2) *Preferred delivery technique as evaluated by treating RTT's* involved in this study.
Study design:	Non randomised clinical interventional study
Planned sample size:	In total, 24 patients will be enrolled into this study.

Medical condition or disease under investigation:	Adult HNC patients receiving radiation therapy as their primary treatment
Participant selection criteria:	Each potential subject must satisfy all of the following criteria to be enrolled in the study. - Patients ≥ 18 years old - Histologically confirmed head and neck cancer. - Patients treated with RT as primary treatment. - An Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0-1. - Each subject must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures required for the study and is willing to participate in the study. - Patients must be willing to comply with treatment plan and other study procedures. Each potential subject must NOT have any of the following criteria to be enrolled in the study. - Patients with significantly altered mental status or with psychological, familial, sociological or geographical condition potentially hampering compliance with the study. - Individual deprived of liberty or placed under guardianship. - Patients who cannot stay still during fraction because of a disorder (e.g. Parkinson's disease)
Treatment:	The treatment of every patient will be divided into different phases: -patients will be irradiated with an open face mask and SS -patients will be irradiated with SS without a mask -patients will be irradiated with a full thermoplastic mask The delivery technique will change for every patient each 5 fractions. The first 8 patients included in the study will have the following schedule: full mask-open mask-no mask-full mask-… The 9^{th} till 16^{th} patient included in the study will have the following schedule: open mask-no mask-full mask-open mask-… The 17^{th} till 24^{th} patient included in the study will have the following schedule: no mask-full mask-open mask-no mask-…
Duration of study:	12 months
Accuracy:	- In-vivo dosimetry using PerFRACTION - Evaluation of intrafractional motion by comparing a CBCT before and at the end of treatment
Statistical methods:	A sample size of 24 patients is estimated to provide 95% power in order to rule out an mean displacement in excess of 2 mm, assuming a significance level of 0.05 (1-sided as testing for non-inferiority).

	Mean displacements and standard deviations will be compared for the different delivery techniques for each patient. Using the method described by van Herck, population mean displacement (MD), systematic (R) and random (r) errors were estimated. CBCT registration results will be analysed in 3-dimensions for each patient; population MD, R and r will be calculated. Paired t- tests will be used to compare the parameters listed above, and timing data (CT and treatment session times). Patient comfort and acceptability questionnaires will be summarised as patient comfort scores ranging from 0 (most comfortable) to 100 (least comfortable). RTT satisfaction questionnaires will be summarised as scores ranging from 0 (most satisfactory) to 100 (least satisfactory). Statistical analyses will be performed using SPSS Statistics.
Trial registration:	This study will be registered on www.clinicaltrials.gov

Funding Source: PENDING

KOM OP TEGEN KANKER, PSYCHOSOCIALE COMMISSIE

ADMINISTRATIVE STRUCTURE

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1. Introduction

1.1 Background & rationale

Head and neck cancer (HNC) is a broad term that encompasses a large number of tumour entities originating from different subsites, such as the nasal cavity, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx and salivary glands.

In Belgium, in the year 2016 (latest data Belgian Cancer Registry), more than 2500 patients were diagnosed with head and neck cancer. (1) In the United States, for the year 2014, there was an estimate of 55.070 new cases of HNC (2). Approximately 60% to 80% of HNC patients present with loco-regionally advanced disease at time of diagnosis. The main treatment options for loco-regionally advanced HNC are (chemo-) radiotherapy (RT) and surgery (often followed by RT). During each RT course, patients are immobilised using a thermoplastic mask (***Figure 1 a.***) to limit the possibility to move during the treatment. Furthermore, this mask enables correct positioning before the start of each RT session.

a. ***b.***

Figure 1. *Full thermoplastic mask (a.) and open thermoplastic mask (b.).*

The use of these masks results in the following disadvantages:

- *They can cause claustrophobia and anxiety. (3, 4, 6)*
- *Intrafractional surface monitoring is not possible with closed masks. (3)*
- *Full-face masks can be very uncomfortable and cause pain by pressure. (5, 6, 7)*
- *The masks don't adapt to weight loss or edema that can occur during radiotherapy.*

Lately, to reduce these side effects, there is an interest in using open face masks (***Figure 1 b.***) in combination with surface scanning (SS). SS is a system which tracks a patient's position before and during RT, to aid in setup and treatment accuracy. Using 3D stereo camera units, the SS tracks the skin surface, and compares it to the ideal position. (4) The combination of an SS and an open face mask therefore enables us to monitor intrafractional movement. (8) This system can then automatically signal the treatment delivery system to pause radiation if the patient moves out of the desired position.

The use of SS together with open face masks for HNC has been studied. An overview of the relevant literature review can be found in ***Table 1.***

Article	Number of participants	Hypothesis	Conclusion
A prospective evaluation of open face masks for head and neck radiation therapy. Wiant D, Squire S, Liu H, Maurer J, Lane Hayes T, Sintay B.	50	To investigate if open mask radiotherapy can be implemented as the new standard for the treatment of HNC.	Immobilization with an open mask works as well as with a closed mask and offers the possibility of real-time monitoring with surface scans.
Migration from full-head mask to "open-face" mask for immobilization of patients with head and neck cancer. Li G, Lovelock DM, Mechalakos J, Rao S, Della-Biancia C, Amols H, et al.	15	To quantitatively characterize the immobilization performance of the open-face mask.	Open-face masks offer advantages in patient comfort and can be used in the treatment of head and neck cancer.
Minimal mask immobilization with optical surface guidance for head and neck radiotherapy. Zhao B, Maquilan G, Jiang S, Schwartz DL.	20	To investigate the feasibility and setup accuracy of minimal face and neck mask immobilization with optical surface guidance.	Minimal mask immobilization offers a streamlined clinical workflow with surface guidance during set-up and treatment. On-board radiographic imaging remains the recommended standard.

Table 1. *Relevant literature concerning the use of open-face masks and OSMS*

Until now, 3 studies have investigated the use of open face masks in combination with SS. Although the results of these studies are promising, even open masks can be problematic for claustrophobic patients or patients with edema or weight loss during RT. Theoretically, it should be possible to combine a less-rigid immobilization with continuous patient motion monitoring to minimize patient discomfort, without losing precision of the treatment (9). Therefore, we want to test the feasibility of irradiating head and neck cancer patients without a mask using SS and compare this technique with open face masks and full thermoplastic masks. The results of this study could possibly help us find a proper alternative for patients who have difficulties with full and open masks. Until now, maskless irradiation has only been investigated in one study with whole brain irradiation (6), so more research is definitely necessary.

In the future, the knowledge we gather with this study regarding SS and maskless irradiation in head and neck cancer patients, will help us to set up new studies eg. the introduction of precise stereotactic radiotherapy for head and neck cancer patients.

1.2 Risks and benefits

- **Possible risk:**

  A longer treatment time in the open face mask or mask-less phase

- **Possible benefit:**

  -Possibly less claustrophobia in the open face mask or mask-less phase

2. Overall study design

The study is designed to evaluate whether irradiating head and neck cancer patients without a mask or with open face masks using SS is comparable to irradiation with full thermoplastic masks in terms of set-up and treatment accuracy and average treatment time.

In total, 24 patients will participate in the study. They are treated with radiotherapy for 35 fractions.

The treatment of every patient will be divided into different phases:
-patients will be irradiated with an open face mask and SS
-patients will be irradiated without a mask but with SS
-patients will be irradiated with a full thermoplastic mask

The delivery technique will change for every patient each 5 fractions.

- The first 8 patients included in the study will have the following schedule:
  full mask-open mask-no mask- full mask-open mask-no mask-full mask
- The 9th till 16th patient included in the study will have the following schedule:
  open mask-no mask-full mask-open mask-no mask-full mask-open mask
- The 17th till 24th patient included in the study will have the following schedule:
  no mask-full mask-open mask- no mask- full mask-open mask-no mask

We chose the number of patients for each group based on the published literature and the power calculation (Table 1).

2.1 Study period

For each participant, the study starts once written consent is provided and is composed by 2 study phases.

Screening phase

Eligibility of patients will be determined according to the inclusion/exclusion criteria as detailed in section 8. Patients are asked complete the validated Dutch claustrophobia questionnaire before start of treatment (see Section 12 and appendix 1).

Treatment phase

Once enrolled, fully eligible patients will start the intended RT according to the standard of care. The RT dose prescription is left to the discretion of the treating radiation oncologist and is the current standard treatment. Patients are asked about their distress level by the treating physician on a weekly basis (see Section 12 and appendix 2). A score of 0-100 is given by using the Subjective Units of Distress Scale.

The set-up and treatment accuracy will be determined by in-vivo dosimetry using PerFRACTION and by the evaluation of intrafractional motion by comparing a CBCT before and at the end of treatment.

The average treatment time will be measured for all treatment fractions.

2.2 Study duration

The start of the study is defined as the first visit for the first participant providing informed consent. Similarly, the end of study (EOS) is defined as the last visit or scheduled procedure shown in the

schedule of assessments for the last participant. Primary study completion is defined as the final date on which data for the primary endpoint are expected to be collected. The study duration is expected to be around 12 months, subject to change on an ongoing basis.

2.3 Study termination

The sponsor reserves the right to terminate any portion of the study at any time. Possible reasons for termination include:

- Safety reasons
- New scientific knowledge becomes known that makes the objectives of the study no longer feasible/valid.
- Unsatisfactory enrolment of participants.

In terminating the study, the sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

3. Study objectives and endpoints

3.1 Primary objective

We would like to investigate whether irradiation with open face masks and SS, and without masks and SS, for patients with head and neck cancer is at least as good as irradiation with a full thermoplastic mask in terms of set-up and treatment accuracy.

3.2 Primary endpoint

1) Set-up and treatment accuracy, determined by in-vivo dosimetry using PerFRACTION, and by the evaluation of intrafractional motion by comparing a CBCT before and at the end of treatment in patients receiving RT with an open mask, without a mask and using a closed thermoplastic mask.

2) Average treatment time for the different deliveries (full mask, open mask, without a mask)

3.3 Secondary objective

Our secondary objective is:

3) to demonstrate that irradiation with open face masks and SS or no face masks and SS for patients with head and neck cancer reduces the patients' levels of distress when compared to irradiation with full thermoplastic masks.
4) to demonstrate that irradiation with open face masks and SS or no face masks and SS is feasible for the treating RTT's.

3.4 Secondary endpoints

3) Level of distress of patients, determined by using the subjective units of distress scale (scale of 0-100).
4) Preferred delivery technique as evaluated by treating RTT's involved in this study.

Our hypothesis for this trial can be best described by the PICO (Patient Intervention Comparison Outcome):

- Patient: patients who are in need of primary treatment with radiotherapy for a histologically confirmed HNC
- Intervention: irradiation with SS and an open face mask; irradiation with SS but without a thermoplastic mask
- Comparison: standard of care treatment, irradiation with a full thermoplastic mask
- Outcome: accuracy of the irradiation (in-vivo dosimetry, intra-fractional motion during radiotherapy); duration of the irradiation in the different groups; results of claustrophobia questionnaires; results of RTT satisfaction questionnaires

4. Study population

4.1 Subject inclusion criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

- Patients ≥ 18 years old
- Histologically confirmed head and neck cancer.
- Patients treated with RT as primary treatment.
- An Eastern Cooperative Oncology Group (ECOG) Performance Status grade of 0-1 as defined in Appendix 3.
- Each subject must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures required for the study and is willing to participate in the study.
- Patients must be willing to comply with treatment plan and other study procedures.

4.2 Subject exclusion criteria

Each potential subject must NOT satisfy any of the following criteria to be enrolled in the study.

- Patients with significantly altered mental status or with psychological, familial, sociological or geographical condition potentially hampering compliance with the study.
- Patients who cannot stay still during fraction because of a disorder (e.g. Parkinson's disease)

4.3 Subject withdrawal criteria and procedures

- The general condition of the patient is too bad to continue the RT
- The patient can withdraw from the study at any moment for any reason

The patients who withdraw will not be replaced.

Specific aftercare for this therapeutic strategy is no different from the current standard of care.

5. Treatment allocation

Patients will be assigned to a study group based on their date of enrolment.

The treatment of every patient will be divided into different phases:
-patients will be irradiated with an open face mask and SS
-patients will be irradiated without a mask but with SS
-patients will be irradiated with a full thermoplastic mask

The delivery technique will change for every patient each 5 fractions.

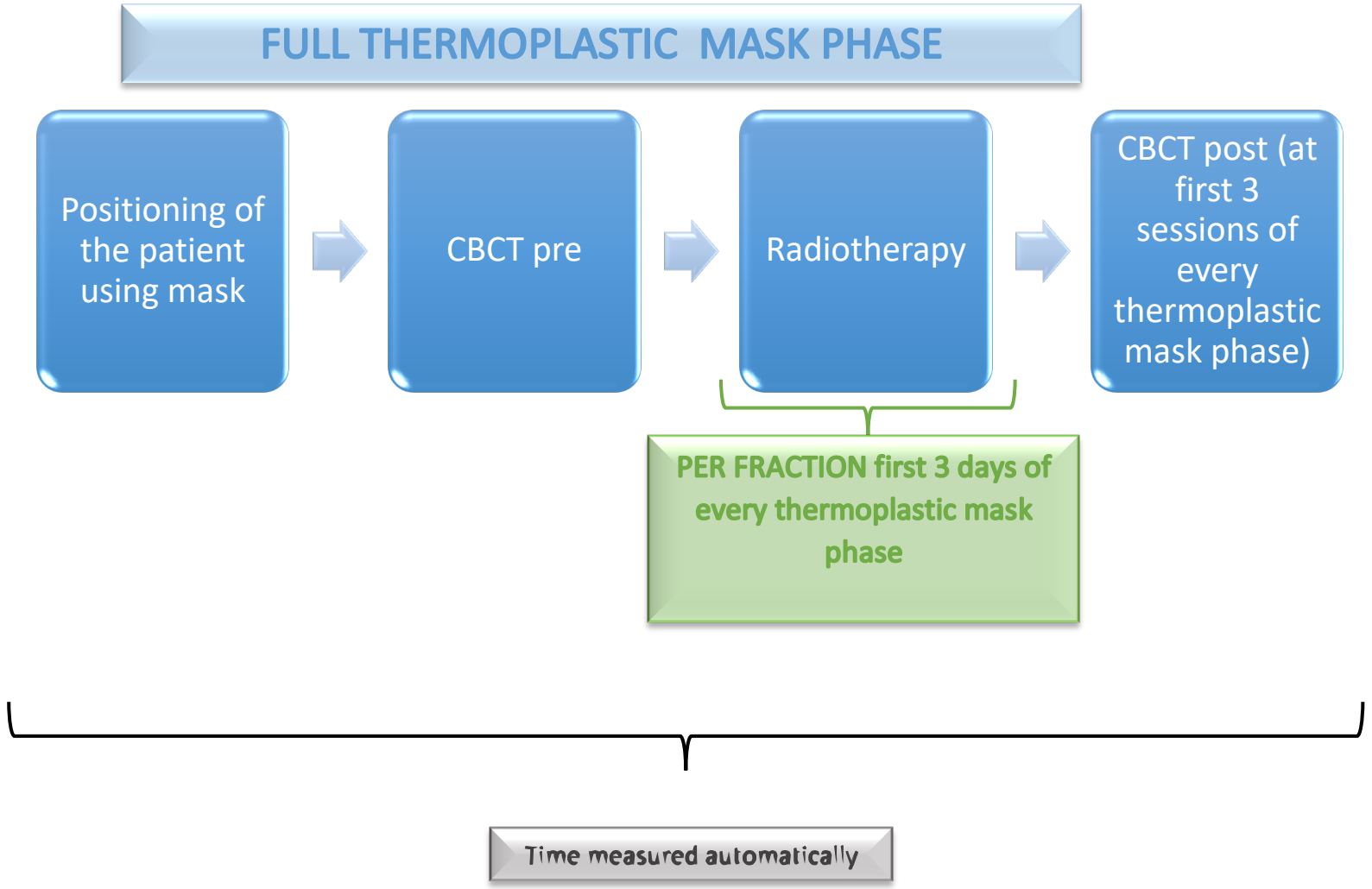
- The first 8 patients included in the study will have the following schedule:
  full mask-open mask-no mask- full mask-open mask-no mask-full mask
- The 9th till 16th patient included in the study will have the following schedule:
  open mask-no mask-full mask-open mask-no mask-full mask-open mask
- The 17th till 24th patient included in the study will have the following schedule:
  no mask-full mask-open mask- no mask- full mask-open mask-no mask

5.1 Assignment of participant numbers

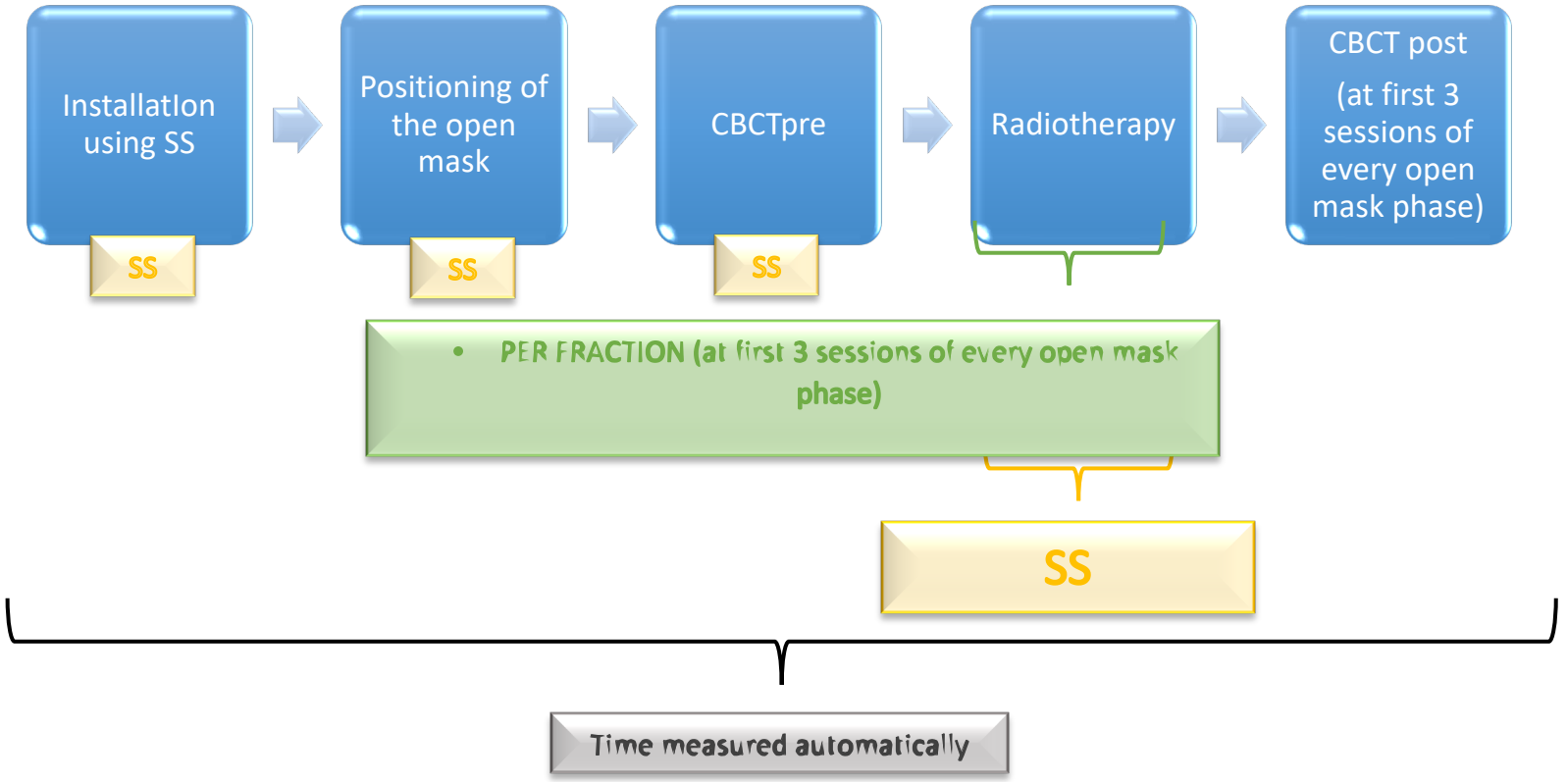
To manage study enrolment, each participant will be allocated a -character participant number comprised of a -digit study site number (01, 02, etc.) and a -digit number incremental per center representing the sequential order in which they are screened (01-001, 01-002, etc.). The -digit participant number will be used to identify the participant throughout the study.

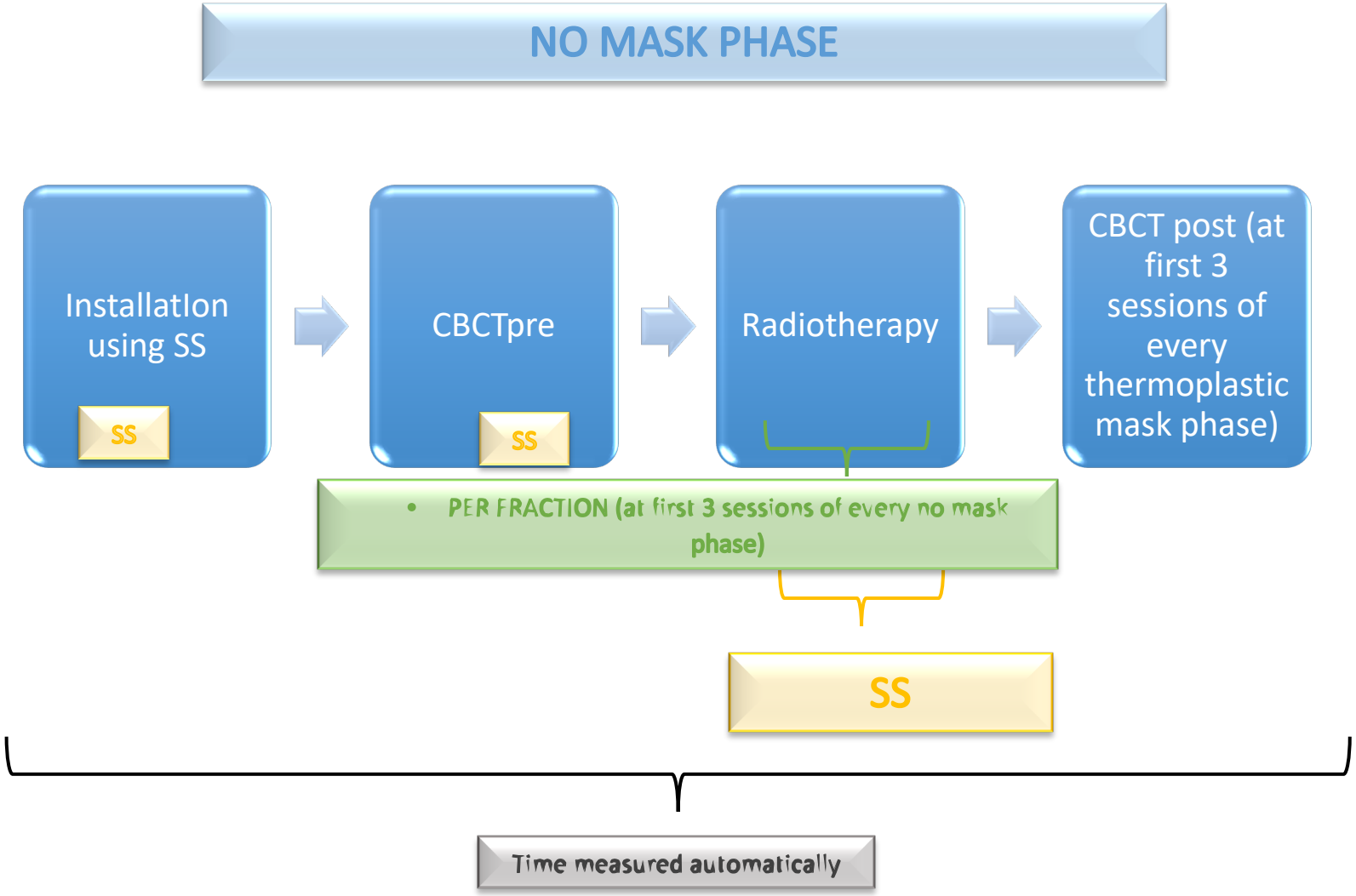
6. Treatments

6.1 Details of study treatment and different phases



OPEN FACE MASK PHASE




NO MASK PHASE
InstallatIon using SS
SS
CBCTpre
SS
Radiotherapy
CBCT post (at first 3 sessions of every thermoplastic mask phase)
• PER FRACTION (at first 3 sessions of every no mask phase)
SS
Time measured automatically

6.2 Prior and concomitant medications

Before and during the period of radiotherapy administration there are no specific medications that are prohibited. We would ask the subject to mention if they took any anxiolytics the day of a session of radiotherapy because this could influence our results. This should be recorded in the CRF.

7. Study assessment

7.1 Time and events schedule

The procedures and assessment to be performed throughout the study are outlined in the time and events schedule.

Table 2. Time and events schedule for all participants

Procedure or assessment		**Screening**	**During treatment**
Informed consent procedure		x	
Eligibility criteria assessment		x	
ECOG Performance Status		x	
RTT appreciation 0-100			Q1wk
Dutch Claustrophobia questionnaire	Appendix 1	x	
Level of distress	Appendix 2		Q1wk
Treatment time			Every treatment session
In vivo dosimetry			Every first 3 sessions of every phase
Evaluation of the intrafractional motion			Every first 3 sessions of every phase

Abbreviations: Q1wk: weekly

7.2 Study procedures

The study procedures are described in subsequent sections

<u>Patient demographics and other screening characteristics</u>

The data that will be collected at screening include:

- Demography (date of birth)
- ECOG performance status (Appendix 3)
- Patient questionnaire: the Dutch Claustrophobia questionnaire
- Use of anxyolitic medication

<u>Accuracy assessments</u>

-using PerFRACTION (in vivo dosimetry)

- using the intrafractional motion determined by the change in position between the CBCT pre and post treatment

<u>Assessment of patients' distress level</u>

-Weekly using the level of distress (see appendix)

Assessment of treatment time

-Will be done automatically using the radiotherapy delivery software

Assessment of RTT preference

- Using score of 0-100

8. Safety monitoring and reporting

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

8.1 Adverse event definitions and classifications

Definitions in Law of May 7, 2004 concerning experiments on the human person:

Adverse event (AE):

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject which does not necessarily have a causal relationship with treatment**.**

Serious adverse event (SAE):

An SAE is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is medically important (medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

Relationship of AEs to the intervention under investigation is assessed using the following scale: related (that is, it resulted from any of the research procedures)/unrelated.

Unexpected AE are events that are not listed in the protocol as an expected occurrence.

Severity criteria: the NCI-CTCAE (version 5.0 or later) will be used to grade the severity of adverse events.

The assignment of the relationship/severity should be made by the investigator responsible for the care of the participant. The sponsor of the study has delegated the assessment of expectedness to the study responsible physician or his delegate. The expectedness assessment will be performed and compared to known complications for this type of radiotherapy.

8.2 Reporting procedures

Period of observation

Table 2: Reporting period for AEs and SAEs

Period	AEs (non-serious)	SAEs
From: Main ICF signature To: Day 1 of the intervention under investigation	Only if related to trial participation	All (regardless of relationship)
From: Day 1 of the intervention under investigation To: 30 days after last treatment	All (regardless of relationship)	All (regardless of relationship)

Reporting

All AEs must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the adverse event to treatment.

The investigator shall report all serious adverse events immediately (<24h), after first knowledge, to the sponsor. Information regarding SAEs will be transmitted to the sponsor using the SAE form, which must be completed and signed by a physician from the study site and transmitted to the sponsor (safetycto@gza.be) within 24 hours.

All SAEs that have not resolved by the end of the study or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- the event resolves
- the event stabilizes
- the event returns to baseline, if a baseline value/status is available
- the event can be attributed to agents other than the treatment or to factors unrelated to study conduct
- it becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

The immediate and follow-up SAE reports shall identify subjects by patient specific study numbers.

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by the treatment;
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated;
- A hospitalization planned for protocol-related treatment or protocol-related procedure as per institutional standard timelines;
- Social and/or convenience admission to a hospital;
- Medical or surgical procedure, e.g., endoscopy, appendectomy; unless the condition that leads to the procedure is an (S)AE.

- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an AE);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

For reported death of a subject, the investigator shall supply the sponsor and the accredited ethics committee with any additional information requested.

The sponsor shall keep detailed records of all adverse events which are reported to him by the investigators. These records shall be submitted to the minister if the experiment is being conducted in Belgium, if he so requests.

Notification of serious adverse events

The sponsor shall ensure that all relevant information about related unexpected serious adverse events that are fatal or life-threatening is recorded and reported as soon as possible to the competent ethics committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected unexpected serious adverse reactions shall be reported to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor. The sponsor shall also inform the other investigators.

Once a year throughout the experiment, the sponsor shall provide the ethics committee with an annual safety report, listing all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety (development safety update report). Regarding those adverse events and serious adverse reactions the Study responsible physician will take all reasonable measures, in consultation with Sponsor, to protect subjects at risk following the occurrence of such events.

9. Data management

9.1 Data collection

Data required by the protocol will be entered in an Excel based database. The PI and Sofie Proost , Maxim Van den Kieboom and Jonathan Michielsen will have acces to this database.
These patients will be numbered and anonymised according to the moment of inclusion. Database will be excel-based and Access-based.

10. Statistical considerations

10.1 Justification of sample size

A sample size of 24 patients was estimated to provide 95% power in order to rule out an excess of 2 mm in mean displacement, assuming a significance level of 0.05 (1-sided as testing for non-inferiority).

10.2 Statistical plan

A sample size of 24 patients was estimated to provide 95% power in order to rule out an excess of 2 mm in mean displacement, assuming a significance level of 0.05 (1-sided as testing for non-inferiority).

Mean displacements and standard deviations will be compared for the different delivery techniques for each patient. Using the method described by van Herk, population mean displacement (MD), systematic (R) and random (r) errors were estimated.
CBCT registration results will be analysed in 3-dimensions for each patient; population MD, R and r will be calculated. Paired t- tests will be used to compare the parameters listed above, and timing data (CT and treatment session times).
Patient comfort and acceptability questionnaires will be summarised as patient comfort scores ranging from 0 (most comfortable) to 100 (least comfortable).
RTT satisfaction questionnaires will be summarised as scores ranging from 0 (most satisfactory) to 100 (least satisfactory).
Statistical analyses will be performed using SPSS Statistics.

10.3 Protocol deviations

All protocol deviations will be assessed and documented on a case-by-case basis before database lock. Important protocol deviations related to study inclusion or exclusion criteria, conduct of the study, non-compliance, participant management, or participant assessment should be described. Protocol deviations will be listed, and significant protocol deviations will be reported to the Ethics Committees (EC).

10.4 Safety analyses

No separate safety analyses are planned.

10.5 Interim analyses

No interim analyses are scheduled.

11. Study management

11.1 Ethics and consent

Regulations and guidelines

The study will be conducted in compliance with this protocol, the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the principles of GCP and all of the applicable regulatory requirements.

Independent Ethics Committees (IEC)

A favourable opinion from the relevant IEC(s) will be obtained before the start of the study.

The IEC will be notified about the EOS and a report summarizing the study results will be sent to the IEC within 1 year after the EOS. If the study is terminated early, the IEC will be notified within 15 days.

Favourable opinion is required for the study protocol, protocol amendments, ICFs, participant information sheets, and advertising materials if any.

11.2 Insurance and indemnification

In accordance with the Belgian law relating to experiments on human persons dated May 7, 2004, the sponsor shall assume, even without fault, the responsibility of any damages incurred by a study patient and linked directly or indirectly to the participation to the study, and shall provide compensation therefore through its insurance.

11.3 Informed consent

For each study participant, informed consent will be obtained in writing before any protocol-related activities commence. As part of this procedure, the investigator or a designated representative must explain orally and in writing, by means of the ICF, the nature, duration, the purpose of the study, the number of visits, the assessments, procedures to undergo, and the action of the treatment in such a manner that the participant is aware of the potential risks, inconveniences, or adverse effects that may occur. Participants should be informed that they may withdraw from the study at any time without any resulting disadvantage and prejudice to their standard treatment care. They will receive all information that is required by national regulations and ICH guidelines.

The participant and the investigator will sign the ICF. A copy will be provided to the participant. The originally signed ICF will remain at the study center and filed in the participant's medical records.

All participants will be insured against injury caused by their participation in the study according to the legal requirements. They will be informed about the insurance and the resulting obligations on their part.

11.4 Data protection

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfil the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

11.5 Discontinuation of the study by the sponsor

The sponsor reserves the right to discontinue the study at 1 center or at multiple centers for safety or administrative reasons at any time. In particular, a center that does not recruit at a reasonable rate may be discontinued. Should the study be terminated, and/or the center closed for whatever reason, all documentation pertaining to the study must be returned to the sponsor or its representative.

11.6 Data management and quality control

Electronic case report forms

The investigator should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the center's study participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete.

All clinical data will be captured via electronic data capture using a web-based tool in compliance with all legislation relevant to electronic data capture (FDA 21 CFR Part 11, Good Clinical Practice).

The investigator's study center staff will enter and edit the data via a secure network, with secure access features (username and password). A complete electronic audit trail will be maintained. The investigator will approve the data using an electronic signature (FDA 21 CFR Part 11), and this approval is used to confirm the accuracy of the data recorded. Electronic CRFs will be used for all participants. The investigator's data will be accessible from the investigator's site throughout the study. The eCRF must be kept current to reflect participant status at each part during the course of the study. The eCRF will not capture personalized data. The investigator must make a separate confidential record of personalized details (name and initials) on the participant identification and enrollment log. All changes to data are done by the investigator or designated site personnel through the electronic data capture system.

It is the responsibility of the principal investigator of the respective center to ensure that all participant discontinuations or changes in treatment entered on the participant's eCRF are also made on the participant's medical records. The eCRFs for any participant leaving the study should be completed at the time of the final visit or shortly thereafter.

Study monitoring and quality assurance

The sponsor will implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of the study with a focus on study activities essential to ensuring protection of participants and the reliability of study results. The quality management system will use a risk-based approach.

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel of the sponsor. Monitoring will be based on a systematic approach and will include site visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, Good Clinical Practice guidelines, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each participant. Note that a variety of original documents, data, and records will be considered as source documents in this study.

The eCRF itself is not to be used as a source document under any circumstances. The study may be audited by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required participant records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate. Relevant data (concomitant medication, and AEs) will be transcribed by the center personnel into the eCRF. The eCRFs for any participant leaving the study should be completed at the time of the final visit or shortly thereafter.

Record retention

The investigator must arrange for retention of study records at the center. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

To meet regulatory requirements, the CRF data will be electronically stored at the data center. The eCRF and audit trail data will be created and provided to the centers in PDF files.

11.7 Use of information and publication

Publications will be coordinated by the study responsible physician. 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.

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Appendices

Appendix 1: Dutch Claustrophobia questionnaire (English translation)

Name:……. Date……

How anxious would you feel in the following situations?

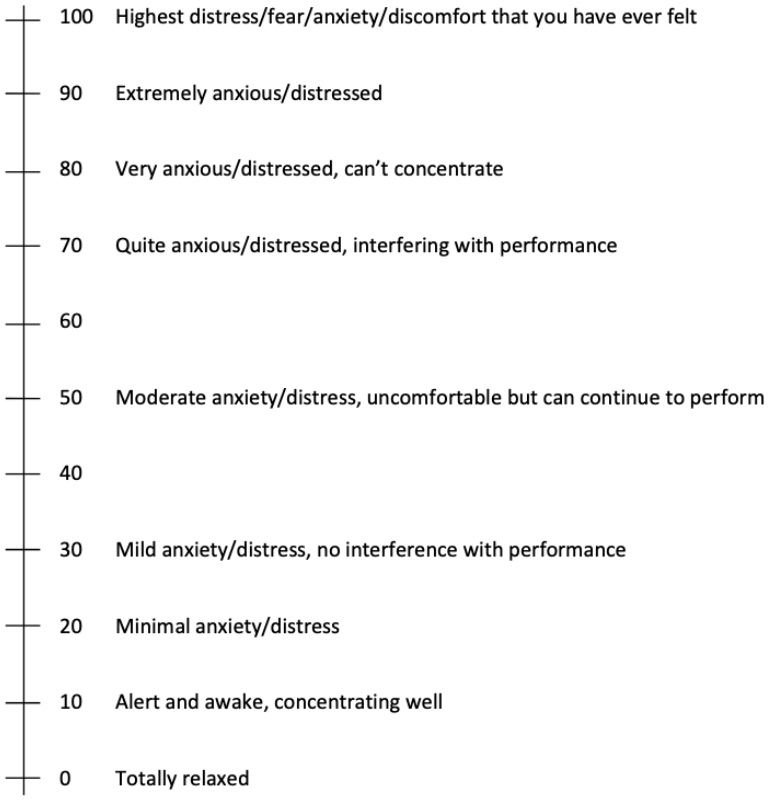
A= Not anxious B= a bit anxious C=Fairly anxious D= very anxious E= Extramely anxious

1. Being restrained in a straight jacket for 15 minutes.
2. Being tied to an immoveable chair.
3. Being tied up with your hands behind your back for 15 minutes.
4. Being handcuffed for 15 minutes
5. Being locked up in a small dark room during 15 minutes
6. Laying in a small sleeping bag which fits tightly around your arms and legs and which is tied at the level of your neck.
7. Laying in the trunk of a car during 15 minutes with sufficient oxygen supply.
8. Wearing clothes that are to small and not being able to remove them.
9. Laying in a closed sleeping bag with your head at the end where your feet should be and not being able to get out.
10. Being locked op in a lit room without windows for 15 minutes.
11. Being in an overcrowded train, stopped between two stations.
12. Noticing the door is jammed on a public toilet.
13. Swimming with a nose clip on.
14. Working underneath the sink for 15 minutes.
15. Standing in an elevator on the ground floor with the doors shut.
16. Trying to catch your breath during heavy exercise.
17. Having trouble breathing through your nose during a bad cold.
18. Snorkeling in a safe practice tank for 15 minutes.
19. Using an oxygen mask.
20. Lying at the bottom of a bunk bed
21. Standing on the third row at a sold-out concert and realizing you won't be able to leave the room before the end of the show.
22. Sitting in the middle of a full row at the movie theater.
23. Working beneath a car for 15 minutes.
24. Standing still during an excursion within an underground mine at the furthest point from the exit.
25. Lying inside a sauna for 15 minutes.
26. Waiting inside of an airplane which stands on the ground while the doors are closed.

Appendix 2: Subjective Units of Distress Scale

The distress thermometer – Subjective Units of Distress Scale (SUDS)

Try to get used to rating your distress, fear, anxiety or discomfort on a scale of 0-100. Imagine you have a 'distress thermometer' to measure your feelings according to the following scale. Notice how your level of distress and fear changes over time and in different situations.



Appendix 3: ECOG Performance Status Grade

Developed by the Eastern Cooperative Oncology Group (Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655)

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.