THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

A SINGLE INSTITUTION PILOT STUDY USING A HEAD AND NECK MASKLESS IMMOBILIZATION DEVICE (MID) FOR PATIENTS BEING TREATED FOR HEAD AND NECK CANCERS OR INTRACRANIAL TUMORS WHO REQUIRE RADIATION THERAPY

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Voichita Bar Ad

Title: Associate Professor

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

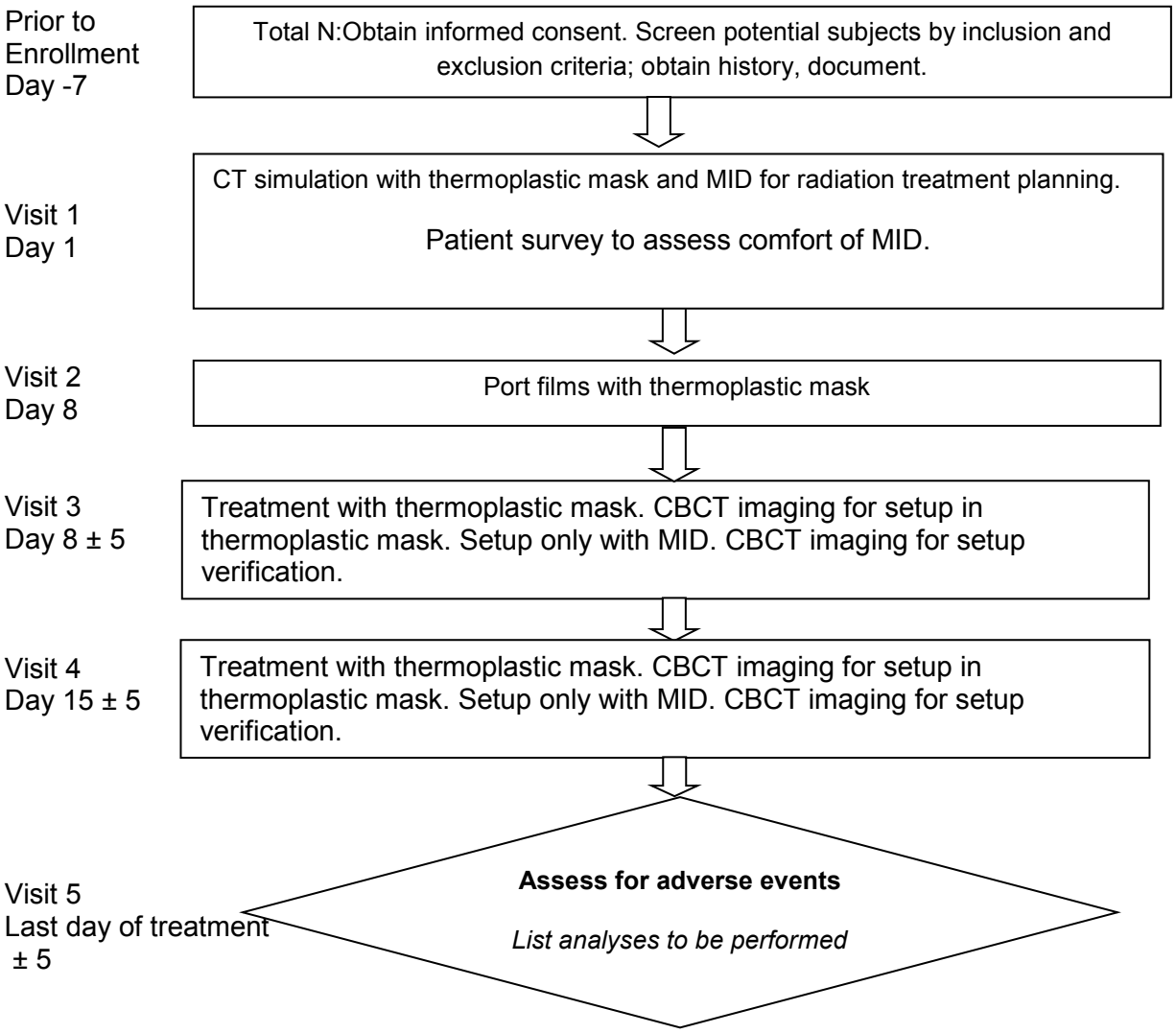
List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem
NCI	National Cancer Institute
SKCC	Sidney Kimmel Cancer Center
CRO	Clinical Research Organization
MID	Maskless immobilization device
CBCT	Cone Beam Computer Tomography
DRR	Digitally constructed radiography
RT	Radiation Therapy
KV	kilovoltage

Study Summary

Title:	*A SINGLE INSTITUTION PILOT STUDY USING A HEAD AND NECK MASKLESS IMMOBILIZATION DEVICE (MID) FOR PATIENTS BEING TREATED FOR HEAD AND NECK CANCERS OR INTRACRANIAL TUMORS WHO REQUIRE RADIATION THERAPY*
Précis:	Patients undergoing radiation therapy (RT) for head and neck cancers or intracranial tumors will undergo CT simulation and port films with the standard thermoplastic mask. On two separate treatment days they will be positioned with the MID after treatment is delivered with thermoplastic mask setup. Cone beam computed tomography (CBCTs) imaging obtained using the RT treating machine will be used to determine degree of setup variance. No RT will be delivered to patients while positioned with the MID.
Objectives:	Primary: The primary objective of this study is to determine the setup accuracy and reproducibility of the MID in patients being treated for head and neck cancers or intracranial tumors who require radiation therapy. Secondary: To assess the patient comfort and quality of life using the MID when compared to the standard thermoplastic mask.
Population:	24 male or female patients who are at least 18 years old, and are being treated for head and neck cancers or intracranial tumors which requires radiation therapy.
Phase:	Pilot
Number of Sites:	1 (Thomas Jefferson University)
Description of Intervention:	Maskless immobilization device (MID) that immobilizes the head and neck of a patient for RT with the use of two straps (one over the forehead and the other over the chin).
Study Duration:	50 months
Subject Participation Duration:	2-7 weeks
Estimated Time to Complete Enrollment:	48 months

Schematic of Study Design:



1 Introduction

1.1 Background Information

There are more than 59,000 men and women in the US diagnosed with head and neck cancer and more than 23,000 new cases of brain tumors every year in US[1, 2]. Moreover, the estimates of brain metastases incidence vary from 20 to 50% in cancer patients. Many of the above patient groups will require radiation therapy (RT) at some point in their care.

Patients receiving RT to the head and neck require immobilization to ensure reproducible setup accuracy. The current standard for head and neck immobilization in RT is a thermoplastic mask[3].The thermoplastic mask conforms to the patient's face and neck anatomy and hardens, allowing a rigid frame that is flush against the patient's body for daily radiation treatment. Specific limitations of this current standard include poor tolerance by claustrophobic patients, requiring daily benzodiazepines or cutting holes in the mask which can compromise setup accuracy. Further, the mask system, while flush against the patient's skin, does allow for different degrees of neck flexion, which can result in error in patient positioning[3]. Currently each mask costs approximately $250[4] and requires replacement if the patient loses too much weight or does not line up properly for daily setup.

Occasionally straps are used to immobilize patients. This can be in the form of adhesive tape for skin cancer treatments using brachytherapy applicators, where the overall position of the patient is not as important as that the applicator covers the skin lesion. The tape serves as a crude immobilization device for the patients head or extremity. Velcro straps are used to immobilize shoulders in patients undergoing radiation treatment to the head and neck. Straps are primarily used when millimeter precision in immobilization is not required, as it is difficult to quantify how much pressure is required to immobilize without causing discomfort to the patient. There is a fine balance between the amount of tension needed to immobilize the patient while maintaining patient comfort.

The proposed MID is a device that will allow the investigator to immobilize the patient without the use of a mask that covers the patient's face. Previous researchers have attempted to use maskless immobilization but the setup precision has historically been questioned[5]. The current technology that is under review for provisional patent status (patent pending) will ensure reproducible immobilization in a non-invasive manner. The intellectual property under review is a device that allows quantification of the immobilization force and vectors. The patient will be positioned on a standard radiation therapy head rest and immobilized with two straps. Strap length will be adjusted by ratchets. Force gauges will be used to quantify how much pressure is applied through the strap, which allows the safe application of the strap, quantification of how much

tension is required for immobilization and reproducibility in subsequent treatment setups. Due to the force gauge quantifying the strap tension the risk of excess tension/pressure on the patient is theoretically less than strap application without the force gauge. This combination of commercially available technologies is the first application of its kind. The strap materials are regular tie down straps constructed of polypropylene, nylon or polyester. They are commercially available and are not the subject of intellectual property. Force gauges are also commercially available and will not have contact with the patient..

In regard to cost, after the initial cost of purchase for the MID (approximately $50), the MID setup may be significantly cheaper than current thermoplastic masks. Each MID will require only two straps of material per patient. The cost may be as low as $5 / patient, in contrast to the current price tag of $250 / patient. Force gauge cost can vary from $20 to $1000. However, they will be part of the radiation table setup and not need to be purchased more than once.

This research will potentially lead to an additional standard of care for immobilization in head and neck RT. It is significantly less costly than the current standard of care. It will be more tolerable to patients with fears of enclosed spaces or objects on their faces. If it is comparable to the thermoplastic mask in regard to setup reproducibility, it may even replace thermoplastic masks.

1.2 **Rationale for the Proposed Study**

The combination of the force gauge and strap for patient immobilization is the subject of intellectual property and does not exist outside this protocol. We propose that this combination allows for a safer application and reproducible immobilization of the patient compared to straps without force gauge quantification of pressure applied. However, the purpose of this study is not to evaluate safety, as the risk to patient with strap immobilization is extremely low. No radiation therapy will be delivered to the patient with MID immobilization.

The MID will be applied to the patient at CT simulation and two points during the treatment schedule, and no treatment will be delivered while the MID is applied to the patient. This will be two arbitrary time points to assess the degree of setup error compared to the gold standard of the thermoplastic mask. The patient population will be those patients being treated for head and neck cancers or intracranial tumors that requires radiation therapy (RT). This population is selected as the treatment fields are simple, and the setup position can be accurately verified by CBCT.

SPECIFIC AIM 1: To assess setup accuracy and reproducibility of the novel MID. We hypothesize that the degree of error with the novel MID will be similar to that of a thermoplastic mask.

SPECIFIC AIM 2: To assess the patient comfort and quality of life using the MID. We hypothesize that patients will have decreased claustrophobia symptoms and/or anxiety when immobilized with the MID compared to the thermoplastic mask.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

Some patients may experience anxiety or claustrophobia but this would likely be to a lesser degree than the thermoplastic mask in which they receive daily radiation treatments. Some patients may experience mild discomfort with the strap application to their foreheads and chins.

CBCTs are used in a regular basis for set up verification and deliver small amounts of additional radiation.

Rationale for additional imaging: No patient will receive radiation treatment with the experimental MID. Patient setup reproducibility and accuracy will be assessed by CBCT. Each day a patient is treated with radiation treatment, they are positioned to replicate the patient setup on the day the CT for radiation treatment planning was obtained. To verify this setup, images such as CBCTs can be obtained and compared to the original CT simulation scan. Since CTs are three dimensional, translational setup errors in the X, Y and Z axis can be quantified.

We need to obtain two additional setup CBCTs on two different treatment days. The CBCT with the MID will allow us to compared the MID setup with the CT simulation scan. The CBCT with the thermoplastic mask will allow us to assess setup error of the gold standard compared to the CT simulation scan. We can then compare the error of the thermoplastic mask with the experimental MID. **Patient safety and treatment will not be compromised as no treatments will be delivered with the MID.**

Safety of additional imaging: CBCTs are obtained by kV imaging. Each CBCT is approximately 5 cGy. The 4 additional CBCTs will add approximately 20 cGy to the patients overall radiation exposure. Patients receiving RT for primary brain tumors will be treated with 300x this dose (6000 cGy). Patients receiving radiation for head and neck cancers may receive doses of 6000-7000 cGy. Patients receiving RT for secondary/metastatic intracranial malignancies will receive 150x this dose (3000 cGy). Thus this additional imaging poses little if any risk to the patient and can ensure more accurate treatment setup and radiation delivery.

1.3.2 Benefits

Potential benefits include decreased anxiety and/or claustrophobia compared to thermoplastic mask.

2 Study Objectives

2.1 Objectives

2.1.1 Primary

To assess the setup accuracy and reproducibility of the MID in patients being treated for head and neck cancers or intracranial tumors who require radiation therapy..

2.1.2 Secondary

To assess the patient comfort and quality of life with the MID compared to the thermoplastic mask.

2.2 Endpoints/Outcome Measures

2.2.1 Primary

The primary endpoints are to assess the setup accuracy and reproducibility with the MID. Accuracy will be measured by quantifying the difference in translational shifts from the daily setup to planning CT scan digitally reconstructed radiograph (DRR). The magnitude of shifts will be compared to the shifts required using the gold standard thermoplastic mask.

2.2.2 Secondary

A secondary endpoint is to assess patient comfort and quality of life with the MID. The measurable outcome will be a questionnaire that assesses the patient's pain, discomfort and level of anxiety when in the MID compared to when in the thermoplastic mask.

2.2.3 Exploratory

3 Study Design

This is a single-institution, pilot study using a MID for RT treatment immobilization of patients being treated for head and neck cancers or intracranial tumors who require radiation therapy.. The patient population will be outpatient based, all of them receiving RT to treat head and neck cancers or intracranial tumors, assessed by CBCT and patient QOL surveys over the duration of their radiation treatment. There will only be a single study arm in which all patients receive RT with the thermoplastic mask but also receive CBCT imaging with the MID to assess the setup accuracy and reproducibility. Patient tolerance of the MID will be assessed through a survey delivered the day of MID use. Setup accuracy will be evaluated by comparing translational shifts required with MID to shifts required with thermoplastic mask. The last QOL evaluation will be at the completion of the patient's radiation treatment. **No radiation therapy will be delivered with MID immobilization.**

3.1 Characteristics

Patients being treated for head and neck cancers or intracranial tumors who require radiation therapy.

3.2 Number of Subjects

24 patients

3.3 Duration of Therapy

2-7 weeks.

3.4 Duration of Follow Up

Only during radiation treatment (up to 7 weeks of therapy)

3.5 Study Timeline

3.5.1 Primary Completion

Accrue patients over 48 months

3.5.2 Study Completion

Completion of accrual and data analysis by 50 months

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

- Patients being treated for head and neck cancers who require radiation therapy or intracranial tumors over a 2 to 7 week period of time.
- Age ≥ 18 years old
- Subjects are capable of giving informed consent or have an acceptable surrogate capable of giving consent on the subject's behalf.
- Provide signed and dated informed consent form

4.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- History of prior trauma or orthopedic surgery to the cervical vertebral column / spine, clinically significant and interfering with the RT planning process, as per the determination of the treating physicians. Patient requires a neck brace for medical reasons
- Skull or bony defect in the area contacting the immobilization straps
- RT delivered by clinical setup only (no CT simulation).

4.2 Strategies for Recruitment and Retention

Patients with head and neck cancers or intracranial tumors who are candidates for receiving RT will be offered the participation in the study, by the treating radiation oncologists. Anticipate screening 30 patients for 24 patients in study.

4.3 Subject Withdrawal

4.3.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The patient will not complete radiation treatment; study closure; patient decision to withdraw from study; or in the judgment of the investigator, continued enrollment in the trial would not be in the best interest of the patient.

4.3.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

Patients will be assessed for any adverse events by treating physician on the last day of radiation treatment, as per the study schema.

4.4 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

5 Study Intervention

5.1 Study Product

Maskless immobilization device (MID)

5.2 Study Product Description

MID is based on two straps that immobilize the head and neck by applying force to the forehead and chin. The product is currently under review for a provisional patent (patent pending).

5.2.1 Acquisition

Product prototype was designed and created in the machine lab in the Department of Radiation Oncology. This is a new device that does not exist in the public domain.

5.2.2 Product Storage and Stability

The Maskless Immobilization Device (MID) will be kept in a locked, secured location within the Department of Radiation Oncology at the Bodine Center. A code will be required to gain entry to the device storage location.

Study Product Accountability

Single device is used for multiple patients. Disposable guards/pads will ensure sanitation between each patient use. Assessing Subject Compliance with Study Product Administration

If patients are undergoing setup with MID for two days during their treatment course then they will be deemed compliant. The MID will not be used during their standard of care treatment. Failure to comply with the MID days will be reported to the treating physician and investigators of this study.

5.3 Study Procedural Intervention(s) Description

Patients will be immobilized in a MID. The device consists of two straps that apply pressure at the patient's forehead and chin. The patient is lying with his/her head resting on a standard radiation head cup. Temporary skin markers (surgical marker and/or radiation setup sticker) will be used to reference the patient setup. Photos will be taken to show position of radiation setup markers. **No radiation therapy will be delivered with MID immobilization.**

5.4 Administration of Procedural Intervention

Radiation therapists, who position patients on the radiation treatment table, will be trained in the application of this device.

5.5 Procedures for Training of Clinicians on Procedural Intervention

Radiation therapists will undergo training for MID use. Their application of the MID to a standardized patient will be evaluated by the investigators prior to independent use.

5.6 Assessment of Clinician and/or Subject Compliance with Study Procedural Intervention

Investigators will directly observe the therapist use the technology on a standardized patient and during the first application on each patient.

6 Study Schedule

CT simulation Day 1	Port films Day 8	Fraction A Day 8 ± 5	Fraction B Day 15 ± 5
Thermoplastic mask immobilization	Thermoplastic mask immobilization + CBCT	Thermoplastic mask immobilization + CBCT	Thermoplastic mask immobilization + CBCT
		RT*	RT*
MID		MID + CBCT	MID + CBCT

*RT is standard of care and will only be given while patients are immobilized with the standard thermoplastic mask.

6.1 Pretreatment Period/Screening

Screening Visit (Day -28 to -1)

- Obtain and document consent from potential subject on consent form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Schedule study visits for individuals who are eligible and available for the duration of the study.

6.2 Enrollment/Baseline

Enrollment/Baseline Visit (Day 0)
Verify inclusion/exclusion criteria.

Record results of complete physical examinations.

6.3 Treatment Period

Visit 1, Day 1
CT simulation with thermoplastic mask. CT simulation with MID. Survey for anxiety and comfort. Symptom directed physical examination. Record any adverse events.

Visit 3, Day 8 ± 5
MID application and setup verification with CBCT. Survey for anxiety and comfort. Symptom directed physical examination. Record any adverse events.

Visit 4, Day 15 ± 5
MID application and setup verification with CBCT. Survey for anxiety and comfort. Symptom directed physical examination. Record any adverse events.

6.4 End of Treatment Study Procedures

Final Study Visit (Final Visit, Last day of RT± 5)

Final visit should occur on the last day of treatment. Patient is assessed for any adverse events. No further follow-up designated.

6.5 Withdrawal Visit/Discontinuation of Therapy

Assessment of any adverse events.

7 Study Procedures and Evaluations

7.1 Study Procedures/Evaluations

Patient medical history will be reviewed from chart and rule out prior neck and/or spine surgery.

A physical examination will be performed, with attention to head and neck range of motion, strength and pain.

8 Evaluation of Safety

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

UAPs are considered to pose risk to subjects or others when they suggest that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2 **Adverse Events**

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

8.1.3 **Serious Adverse Events**

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2 **Safety Assessment and Follow-Up**

The only portion of this study considered to be investigational is the maskless immobilization device (MID). Therefore, the only adverse events that will be reported are those related to the use of the MID.

The PI will follow adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2 Safety Assessment and Follow-Up.

The only portion of this study considered to be investigational is the maskless immobilization device (MID). Therefore, the only adverse events that will be reported are those related to the use of the MID.

8.3.1 Relationship to Study Intervention

The relationship to study device (MID) or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

8.3.2 Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

8.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

8.4 Safety Reporting

The only portion of this study considered to be investigational is the maskless immobilization device (MID). Therefore, the only adverse events that will be reported are those related to the use of the MID.

8.4.1 Unanticipated Problem Reporting to IRB

All incidents or events that meet criteria for unanticipated problems (UAPs), as defined in Section 8.1.1Unanticipated Problems, require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to subjects or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 5 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to subjects or others will be submitted to the IRB at the next continuing review.

8.4.1 Adverse Event Reporting to IRB

Grade 1 AEs are not required to be reported to the IRB.

Grade 2 AEs will be reported to the IRB at the time of continuing review if, in the opinion of the investigator, they represent events that exceed expected frequency or in some other way are judged to be unexpected and possibly associated with increased risk.

Other adverse events will only be reported if deemed related to the IRB.

8.4.2 Serious Adverse Event Reporting to IRB

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly or definitely related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will not be reported.

Grade 5 AEs that are deemed unrelated to the study will not be reported.

8.4.3 Reporting of Pregnancy

No patients receiving radiation therapy should be pregnant. Department policy requires negative pregnancy test prior to starting radiation therapy. No additional protocol effort needed.

8.5 Halting Rules

Study will be halted in the event of one serious adverse event definitely or probably related to the MID.

9 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC).The DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the Clinical Trials Oversight Committee (CTOC).

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC).The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the DSMP.

11 Statistical Considerations

11.1 Study Hypotheses

Primary objective: To establish that the new device is no worse than the old device in term of the setup accuracy and reproducibility. Accuracy will be measured by quantifying the difference in translational shifts from the daily setup to planning CT scan digitally reconstructed radiograph (DRR). The magnitude of shifts will be compared to the shifts required using the gold standard thermoplastic mask.

Secondary objective: To establish that the new device is no worse than the old device in term of increasing patients' comfort and reduce patients' anxiety. The measurable outcome will be a questionnaire that assesses the patient's pain, discomfort and level of anxiety when in the MID compared to when in the thermoplastic mask.

11.2 Analysis Plans

For the primary objective, the magnitude of the single vector that depicts the degree of setup discrepancy from CT simulation will be collected for each patient on each day the MID is applied (for both the thermoplastic mask and the MID). The 90% lower

confidence limit of the absolute discrepancy, as well as the 90% higher confidence limit of the standard error, will serve as a conservative estimate of the mean and standard deviation. Based on literature, the thermoplastic mask results in a need for translational shifts on average of 3.5mm with a standard deviation of 1.2mm[6, 7]. We propose to use a total of 24 patients in the pilot study aiming to establish that the new device is no worse than the old device with a non-inferiority margin of 0.5mm, assuming the new device requires a mean translational error adjustment of patients by 2.5mm with the standard deviation of 1.2mm at 91% power and a Type-I-Error rate of 5%.

For the secondary objective, we will collect the preference survey scores for the thermoplastic mask versus the MID (survey results) from the same patients participated in the primary objective. The preference scores will be compared using cumulative logistic regression model.

11.3 Sample Size Considerations

Sample size calculation for the pilot study has been provided in Section 11.2.

12 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of subject information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity. The only source documents outside of standard medical records available in the EMR will be the patient surveys and record of setup measurement shifts.

13 Quality Control and Quality Assurance

The PI or a Co-I's will be present at the time of CBCT for patients undergoing MID placement for the first placement. Radiation therapists will be supervised by the PI or a Co-I for at least 2 MID placements, and shown proficiency in its use (correct application and patient setup) before they are not supervised.

Translational shifts will be verified by the PI or a Co-I and recorded in a secure electronic spreadsheet. Entries will be verified by radiation therapists. Surveys will be reviewed by clinic nurses to ensure all questions have been completed. Survey data will be recorded.

14 Ethics/Protection of Human Subjects

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline

to participate in this study. The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children are excluded from this study as they often require general anesthesia or sedation during radiation therapy to tolerate the standard thermoplastic mask. Both males and females patients with head and neck cancers or intracranial tumors who require RT will be eligible for the trial.

14.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

14.6 Future Use of Stored Specimens and Other Identifiable Data

Survey data will be held in a secure network drive until 3 years after the completion of the study.

15 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Data will be entered into an electronic spreadsheet by a study team member and verified by a Radiation Therapist. Data will be stored on password protected computers on internal network drives. Survey responses will be inputted electronically by a study team member. Electronic copies of records will be kept for 3 years after completion of study.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2 Data Capture Methods

As described in 15.1, data will be recorded electronically and stored on a password protected, secure network drive.

Types of Data

Translational data and questionnaire data will be collected.

15.3 Study Records Retention

Study records will be maintained for at least three years.

15.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study subject source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

16 Study Finances

16.1 Funding Source

Study will be financed in cooperation with the Department of Radiation Oncology and Thomas Jefferson University Hospital Innovation Pillar.

16.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

16.3 Subject Stipends or Payments

Subjects will not receive any stipends or payments for participation in this study.

17 Publication and Data Sharing Policy

The PI will have primary oversight and responsibility for the publication of these trial results. As this is a small feasibility study it is not required to be reported to the FDA. There is no NIH funding involved in this trial so it is not subject to NIH public access guidelines.

18 Literature References

1. Head and Neck Cancer - Statistics [Internet]. CancerNet [cited 2015 Aug 18]

Available from: http://www.cancer.net/cancer-types/head-and-neck-cancer/statistics

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3. Donato K, Leszczynski K, Fleming K: A comparative evaluation of two head and neck immobilization devices using electronic portal imaging. Br J Radiol 79:158–161, 2006

4. Thermoplastics [Internet][cited 2015 Aug 18] Available from:

http://www.civco.com/ro/products/Thermoplastics.htm

5. Gevaert T, Verellen D, Tournel K, et al: Setup Accuracy of the NovalisExacTrac 6DOF System for Frameless Radiosurgery. Int J RadiatOncol 82:1627–1635, 2012

6. Weltens C, Kesteloot K, Vandevelde G, et al: Comparison of plastic and Orfit® masks for patient head fixation during radiotherapy: Precision and costs. Int J RadiatOncol 33:499–507, 1995

7. Amelio D, Winter M, Habermehl D, et al: Analysis of inter- and intrafraction accuracy of a commercial thermoplastic mask system used for image-guided particle radiation therapy. J Radiat Res (Tokyo) 54 Suppl 1:i69–76, 2013

Appendices

APPENDIX A: SCHEDULE OF EVENTS

Procedures		Screening /Baseline (Day –28 to)	Study Visit 1 (Day 1)	Study Visit 3 (Day 8 ± 5)	Study Visit 4 (Day 15 ± 5)	Visit 5 Last day of treatment ± 5 Days
Signed Consent Form		X				
Assessment of Eligibility Criteria		X				
Review of Medical		X				
CT Simulation[A]			X			
Study Intervention (MID)[B]			X	X	X	
Questionnaire			X	X	X	
Physical Examination	Complete	X				
	Symptom-Directed		X	X	X	
Assessment of Adverse Events				X	X	X

A. CT Simulation will be with both thermoplastic mask and with MID
B. Setup verification for MID application will be done with CBCT. No treatment to be given to patients with MID immobilization.

APPENDIX B: PROMIS

PROMIS - Ca Item Bank v1.0 - Emotional Distress - Anxiety

Emotional Distress-Anxiety

Please respond to each item by marking one box per row.

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
EDANX27	I felt something awful would happen	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX05	I felt anxious	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX12	I felt upset	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX55	I had difficulty calming down	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX02	I felt frightened	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX33	I felt terrified	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX08	I was concerned about my mental health	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX47	I felt indecisive	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX18	I had sudden feelings of panic	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX26	I felt fidgety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX07	I felt like I needed help for my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS - Ca Item Bank v1.0 - Emotional Distress - Anxiety

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
EDANX30	I felt worried	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX46	I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX51	I had trouble relaxing	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX54	I felt tense	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX03	It scared me when I felt nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	Many situations made me worry	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX09	I had unpleasant thoughts that wouldn't leave my mind	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX39	I worried about dying	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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