MSK PROTOCOL COVER SHEET

Feasibility Study of a Hyperspectral Imaging System in Detection of Human Skin Perfusion and Oxygenation

Principal Investigator/Department: Michelle Bradbury, MD/Radiology

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an open observational study being done to test the feasibility and reproducibility of a hyperspectral camera system (HCS) in human skin perfusion. Oxygenation detection will be evaluated, resulting in selection of spectral bands, which could be used in clinical practice. Eight healthy volunteers will be included.

Feasibility and reproducibility of a hyperspectral camera system in human skin perfusion and oxygenation detection will be evaluated, resulting in selection of spectral bands, which could be used in clinical practice.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

To investigate the feasibility, applicability, and reproducibility of a novel hyperspectral camera system in perfusion and oxygenation detection in healthy volunteers.

Secondary Objectives:

- To explore the effect of occlusion-reperfusion of the brachial artery on cutaneous blood flow as assessed by a hyperspectral camera system.
- To explore the effect of applying topical vasoconstrictors / vasodilators on the cutaneous blood flow as assessed by a hyperspectral camera system.
- Selection of relevant spectral bands for oxygenation and perfusion detection.

3.0 BACKGROUND AND RATIONALE

Restoring normal functioning and tissue healing after surgical intervention is, among others, critically dependent on tissue perfusion. Insufficient perfusion with oxygenated blood could result in ischemia and subsequent tissue damage. An important clinical problem is anastomotic leakage, which is one of the most serious complication after gastrointestinal surgery. Anastomotic leakage has a prevalence varying between 1 and 19% and a mortality of 6 to 22% in patients with colorectal cancer [1-5]. Hence, adequate bowel anastomosis is important to prevent leakage. As tissue perfusion is one of the most important risk factors for anastomotic leakage it appears that assessment of perfusion, particularly upon establishment of the anastomosis during surgery, can contribute to better surgical outcomes.

Currently, evaluation of tissue perfusion during surgery can be performed with NIR fluorescence imaging by intravascular injecting indocyanine green (ICG) as fluorophore. Several clinical trials showed good results in evaluating the perfusion of bowel anastomoses and skin flaps used for reconstructive surgery [6-8]. Other optical

techniques, which do not require administration of contrast agents, have also been used to evaluate tissue perfusion and oxygenation. Optical coherence tomography showed the capability to detect in vivo oxygen saturation levels by using the optical absorption coefficient differences between oxygenated and deoxygenated haemoglobin [9]. Laser Doppler imaging can also be used to measure blood flow, but lacks resolution to assess flow in individual vessels [10]. Laser speckle imaging is able to detect individual moving particles such as blood cells. The movement these cells are related to the blood flow velocity, which can be displayed in real-time. Hence, the technique can be used for blood perfusion mapping.

An emerging technique is hyperspectral imaging, which is capable to detect the scattering and absorption of light delivered to the tissue, caused by inhomogeneity of biological structures, such as haemoglobin, fat or water [11]. In vivo real-time imaging of the perfusion is currently not possible, however snapshot imaging was used to evaluate oxygen levels in the retina, which was quite complex, especially the part of data processing [12, 13]. Recently, a novel hyperspectral imaging camera (Quest Medical Imaging BV, Middenmeer, The Netherlands) has become available as prototype. This device allows non-invasive measurement of skin blood flow, oximetry and (vascular) anatomy, only based on the endogenous contrast of the tissue. Therefore it could be used to obtain non-invasively information about the (superficial) anatomical structures and moreover to measure the microvascular condition.

However the capability of this device to pick up physiological changes is unknown. To validate this hyperspectral camera system (HCS) for measuring skin blood flow and vascular anatomy the following study is proposed:

- Measurement of forearm skin blood flow before, during and after occlusion of the brachial artery;
- Measurement of local changes in skin blood flow after applying a local capsaicin-based cream (local vasodilator);

Read outs from the HCS after local application of capsaicin-based cream will be compared to measurements of an untreated area of the forearm. Furthermore, the changes in these measurements will be evaluated over time..

<u>Hyperspectral camera system:</u>
Hyperspectral imaging is a non-invasive optical technique, using halogen light as a light source, which is also widely used in commercially available light sources. Halogen light could produce some heat, however imaging will be performed on a distance of 50 centimetres. The technology used in this camera, is partially comparable to the technology used in Diffuse Reflectance Spectroscopy, which has been used in diverse clinical studies in the Netherlands Cancer Institute without reporting of any side effects during the measurements [17, 18].

<u>Summary of findings from non-clinical studies</u>

The HCS is recently developed and is one of the first camera systems which is expected to create two-dimensional imaging of tissue perfusion based on endogenous tissue contrast, which is far beyond the current state of the art. This study will be the first clinical study in human volunteers and no findings of earlier performed non-clinical studies are available.

We expect no side effects, because this technique only uses halogen light as light source, which is also widely used in commercially available light sources. The sensors used in this camera, are partially comparable to the sensors used in Diffuse Reflectance Spectroscopy. In the Netherlands Cancer Institute good results in tissue characterization and tumor detection were achieved, however this technique is only capable to perform point measurements and could therefore not used during surgery in the future. They also showed that no side effects occurred during and after the measurements [17, 18].

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This study is a non-therapeutic open observational trial, which evaluates the feasibility of the hyperspectral camera system (a non-significant risk device) in evaluation of the tissue perfusion and oxygenation in different circumstances. The exploratory aim of this study is to select relevant spectral bands for oxygenation and perfusion detection, which can be used for further camera development and consequently in clinical practice. Eight healthy volunteers, without any medication use and without any relevant medical history will be included in this study. Subjects will be enrolled following confirmation of study eligibility (section 5.0) which will be checked at baseline. Reproducibility will be validated by performing the following HCS measures:

- Basal blood flow
- Blood blow upon occlusion-reperfusion brachial artery
- Blood flow after applying capsaicin-based cream
- The room temperature, which could influence the skin perfusion will also be measured.

For the secondary endpoints, hyperspectral measures of:

- basal blood flow / oximetry
- blood flow /oximetry upon occlusion-reperfusion brachial artery
- Blood flow / oximetry after applying capsaicin-based cream

Reproducibility will be validated by the HCSmeasure only, at both time points that the HCS is used.

Explorative endpoint:

The explorative endpoint of the study is to see if a selection of spectral bands, specific for tissue perfusion and oxygenation (selected after data processing of above mentioned measurements) can be achieved.

4.2 Intervention

The capability of the HCS in detection of tissue perfusion and oxygenation in eight human volunteers during different circumstances: before/after occlusion brachial artery, before/after application capsaicin-based cream..

Quest Hyperspectral imaging system

The HCS is not approved by the US Food and Drug Administration. The device qualifies as non-significant risk because it is not used as an implant, nor is it used to sustain human life, nor will it be used in diagnosing, curing, mitigating or treating disease and does not present a potential for serious risk to the health, safety, or welfare of a subject.

The device is designed for medical applications and has optimized optics for spectral analysis of biological compounds. In this camera 3 sensors are combined for optimal spectral imaging. For 2D reference, and to facilitate annotating the data, a high resolution (full HD) color image, recorded with an RGB-sensor, is included with each hyperspectral dataset. The spectral bands are acquired using a 4x4 mosaic sensor for the spectral range of 470 – 630 nm, this sensor is referred to as the VIS-sensor. The NIR-sensor is a 5x5 mosaic sensor with a spectral range of 600 – 950 nm (see Figure 1 for an impression of the transmission bands of the sensor pixels). The color image is co-registered with the hyperspectral data with subpixel accuracy, making accurate data fusion and visualization methods possible.

This hyperspectral camera is based on a tiled-filter approach where pixels are individually filtered with narrow Fabry-Pérot bandpass filters. This method allows real-time imaging at video frame rates without the need to scan in either the spatial dimension (e.g. moving the camera) or the spatial dimension (e.g. changing the pass-through characteristics of an optical filter).

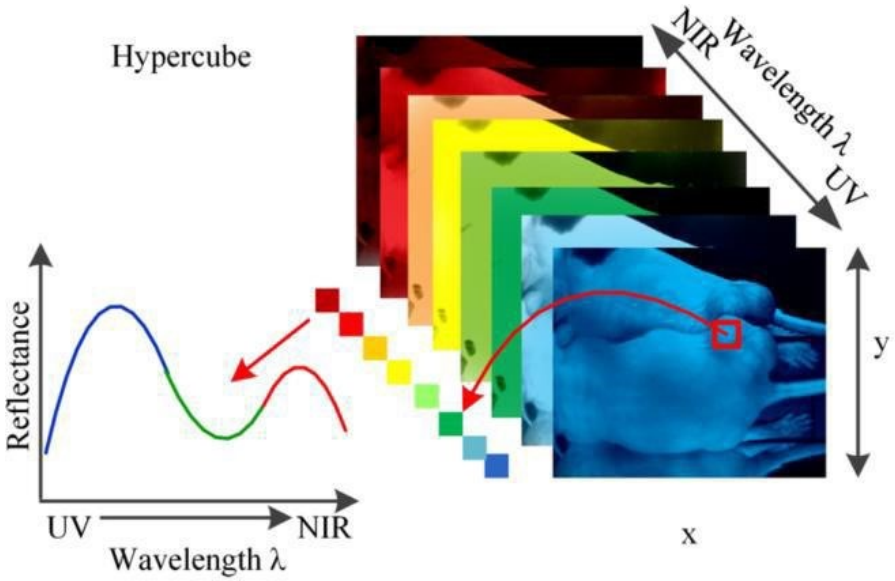
The Quest hyperspectral imaging system has 41 spectral bands, equally distributed in the visible-near infrared (VIS-NIR) range of the electromagnetic spectrum (450 – 950 nm). The time it takes to capture the hyperspectral images and obtaining feedback from the instrumentation is around 2-3 seconds, which is nearly real time. The field of view is 10 x 10 centimeter, which makes this camera system suitable for clinical use in the future. It delivers images with a 10 frames per second framerate.

The device has been supplied to MSK by Quest Innovations.

Data analysis HCS

After each measurement of a specific tissue part, a 3-dimensional hypercube with a corresponding graph could be created after data processing as illustrated in this figure [11].

The HCS consists of three sensors, creating three images, that have to be merged to a 3D datacube. Before merging, the images has to be analysed. In general, hyperspectral image analysis will consist of preprocessing, feature extraction and selection, and classification. Noise could be removed by preprocessing part of data analysis by diverse denoising techniques. After denoising, the images could be merged to a 3D datacube. Afterwards, feature extraction will be applied to select clinically relevant spectral bands for perfusion and oxygenation measurements. Finally, principle component analysis is used to reduce redundant information in the bands of hyperspectral imagery while preserving as much of the variance in the high dimensional space as possible [11].



Non-Investigational products:

1. Capsaïcin crème FNA 0,75 mg/g Capsaicin-based cream is a selective 'transient receptor potential vanilloid 1-receptor' (TRPV1) agonist. It is registered for use in the treatment of local itch, post herpes neuralgia or diabetic polyneuropathy. The compound has been selected because of it induces release of vasoactive neuropeptides causing vasodilatation.

The medication will be administrated cutaneously, according to the prescription. We will use the commonly used concentration of cream for clinical practice.
The cream will be administrated cutaneously. Capsaicin cream we will use a 0.075% dosage.

Thecream will only be used during this feasibility study to induce vascular changes in healthy human volunteers. The cream will be supplied by the MSK pharmacy as per standard single patient ordering procedures. We aim to detect these small vascular changes with the hyperspectral camera. If the camera is able to detect these changes, it has the potential to detect small vascular changes in patients with bad vascular perfusion for whatever reason (vascular diseases, surgical intervention etc.). We will emphasize that the medication is not necessary for using the hyperspectral camera, however it is only used to induce vascular changes.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

5.1 Subject Inclusion Criteria

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

- Healthy volunteers, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of any active or chronic disease following a detailed medical and surgical history.
- Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg.
- Able to participate and willing to give written informed consent and to comply with the study restrictions.

5.2 Subject Exclusion Criteria

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

- History or symptoms of any significant disease including (but not limited to), neurological, psychiatric, endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.
- Systolic blood pressure (SBP) greater than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.
- Use of any medications (prescription or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary supplements within 21 days of study drug administration, or less than 5 half-lives (whichever is longer). Exceptions are paracetamol (up to 4 g/day). Other exceptions will only be made if the rationale is discussed and clearly documented between the Investigator and the sponsor.
- Concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
- Smokers as defined by any of the following criteria:
    - Reported smoking of cigarettes within 12 months prior to screening; occasionally a cigarette is allowed, but not within 24 hours of the measurements.
- Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug allergies (non-active hay fever is acceptable).

- Unwillingness or inability to comply with the study protocol for any other reason.

6.0 RECRUITMENT PLAN

Enrollment in this study will be open to all MSK employees to act as healthy volunteers provided they meet eligibility criteria. Every effort will be made to include women and minorities in the research study. Employees who provide consent willfully and voluntarily may participate as a healthy volunteer once. The volunteers will primarily be recruited from members of the Department of Radiology who are willing to participate via word of mouth. To prevent departmental researchers from feeling pressured into participating in this study (i.e., where there is a status relationship), it is a Department policy to strictly forbid a person to ask a subordinate employee to participate in an evaluation. This policy is described to each new researcher as part of their research training, and all members are routinely reminded of this study policy during research meetings. Participation will occur outside of the employee's usual working hours.

Participants will be offered a $50 dollar gift card for their participation.

During the initial conversation between the investigator/research staff and the participant, the participant may be asked to provide certain health information that is necessary to the recruitment and enrollment process. If the participant turns out to be ineligible for the research study, the research staff will destroy all information collected on the participant during the initial conversation and medical records review. ..

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7.0 ASSESSMENT/EVALUATION PLAN

Subjects will participate on 2 similar study days, separated by a minimum of 3 days and maximal 28 days. Measurements will be assessed by the HCS and will take maximum 2 hours.

Pre-treatment evaluation (after study consent and registration of volunteers):

- Medical history review
- Weight

Once eligibility is confirmed:

- Blood pressure
- Heart rate
- Room temperature

On study procedures to be followed:

1) The volunteer is installed at the test location (Pre-surgical Center, M-6) at the main hospital

2) Before starting the measurements, the blood pressure, heart rate and room temperature are measured to establish the baseline characteristics.

3) The volunteer is asked to stretch both forearms near to each other in sitting position.

4) The blood flow is measured by the HCS at baseline on both forearms (Total field of view: max. 10 x 10 cm)

5) After baseline measurements the flow is measured on either the right or left forearm during five minutes occlusion (a blood pressure cuff will be used) of the right brachial artery and during five minutes of reperfusion after occlusion.

6) After taking these measurements, there is a short break of 5 minutes, to save all measurements.

7) Local capsaicin-based cream is administrated on the same forearm on an area of 3 x 3 cm, on a distance of 5 cm under the radiocarpal joint.

8) 30 minutes after application of the crème, crème is removed from the skin.

9) For obtaining optimal flare, 20 minutes after removing the crème, the perfusion is measured by HCS for 5 minutes.

10) Region with administrated local capsaicine-based cream is compared to control regions located on the same forearm,

11) After 10 minutes the procedure is finished.

Concomitant medications and alcohol/caffeine consumption

The use of the following concomitant medications is prohibited: no prescription medications, over-the-counter (OTC) medications, vitamin, herbal and dietary supplements will be permitted within 14 days prior to study drug administrations, or less than 5 half-lives (whichever is longer, and during the course of the study. The following exceptions are applied:

- paracetamol (up to 4 g/day).
- Other exceptions will only be made if the rationale is discussed and clearly documented by the investigator

Both alcohol and caffeine consumption could influence the skin perfusion [14, 15]. Therefore, alcohol and caffeine consumption is prohibited within 12 hours preceding both study days. Before starting the measurements, the blood pressure, heart rate and room temperature will be measured to establish the baseline characteristics.

8.0 TOXICITIES/SIDE EFFECTS

HCS: No side effects were expected, because imaging of the skin perfusion is a non-invasive procedure. This technique only uses halogen light as light source, which is also widely used in commercially available light sources.

Capsaicin cream (FDA approved): The concentration used for this study is 0.075%, which is commonly used in clinical practice. Some side effects were reported by using capsaicin-based cream. In 0.01-0.1% hypertension, first-degree AV block and tachycardia were reported, which were the most dangerous complications. Other complications, such as local skin irritation, local pain and erythema are more commonly seen. No interactions with other drugs were reported.

9.0 PRIMARY OUTCOMES

Assessment	Screening	Visit 1	Visit 2 (to occur between 3 and 28 days after Visit 1)
Medical History	X		
Weight	X		
Blood pressure		X[1]	
Heart Rate		X[1]	
Room temperature		X[1]	
HCS measurements		X[2]	X
Creme applications		X	X

[1]Before starting HCS measurements, blood pressure, heart rate and room temperature will be measured to establish baseline characteristics.

[2]Blood flow is measured by HCS and on both forearms at baseline (Total field of view: max. 10 x 10 cm). After baseline measurements the flow is measured on either the right or left forearm during five minutes occlusion of the right brachial artery and during five minutes of reperfusion after occlusion. After taking these measurements, there is a short break of 5 minutes, to save all measurements.

The detailed study procedures to be followed are outlined in section 7.0.

10.0 CRITERIA FOR REMOVAL FROM STUDY

Participants may withdraw from the study at any time. If at any time the participant is deemed ineligible for the study, they will be removed from the study.

11.0 BIOSTATISTICS

Primary study parameter(s)
Reproducibility is measured by performing the measurements on two different days in the same study population. Sample T-tests will be used for comparison of the perfusion

measured by the HCS system and room temperature in the eight recruited human volunteers. The intra-subject variability over the two measurement moments will be established by calculation of the coefficient of variation.

Secondary study parameter(s)
For spectral measurements no specific statistical analysis is performed. It is mainly a part of data processing as described in the study design protocol section 4.0.

Leiden University Medical Center (LUMC) is utilizing their own protocol under their own regulatory body oversight, and conducting separate but similar protocols. LUMC data will pooled with our data for analysis.

The PI of this study will be sharing de-identified data with an external collaborator at Leiden University Medical Center for the purpose of data analyses. Anonymized images taken from the hyperspectral camera will be electronically sent to Quest Medical Imaging for analysis.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

12.2 Randomization

Not applicable.

13.0 DATA MANAGEMENT ISSUES

Radiology research staff will be assigned to manage this study. Radiology clinical research coordinator and a regulatory research associate will be responsible for protocol compliance, data collection, data abstraction and entry, data reporting, regulatory monitoring, adverse event tracking and reporting, SAE reporting, regulatory submissions, problem resolution and prioritization, and coordinate the activities of the protocol study team.

Source documentation will be available to support the computerized patient record. All research material from this study will be handled with the same confidentiality as patients' medical data records.

MSK data will be collected in a secure, restricted departmental database. The PI of this study will be sharing de-identified data with an external collaborator at Leiden University Medical Center for the purpose of data analyses. Anonymized images taken from the hyperspectral camera will be electronically sent to Quest Medical Imaging for analysis.

Leiden University Medical Center (LUMC):

As a similar study is being done at LUMC, after the study is complete at MSK, we plan to share de-identified MSK data with LUMC for data analyses and to combine results. No participant identifiers to be shared.

Section 13.1 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be two separate protocol documents and each site will utilize their own locally approved document.

Participating sites that are conducting data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

13.1 Quality Assurance

Throughout the life of the study, the study team comprising of the PI, key investigators and Radiology research staff will review data and compliance regularly. Accrual rates, review of adverse events, potential serious adverse events, and any pontential challenges will be regularly discussed. Regular registration reports will be generated to monitor accruals, registrataion, data accuracy and completeness. Routine data quality reports will be generated to assess missing data and inconsistencies. Potential problems will be brought to the attention of the PI and Radiology research management for discussion and action. Random sample data quality audits will be performed and evaluated regularly.

13.2 Data and Safety Monitoring

The study investigators will be responsible for ensuring the safety of the study participants. The investigators will stress the importance of reporting adverse events to the participants, and the investigators will assess for adverse events at each instance of contact with the participants. Should adverse events occur, the study investigators will document these appropriately and report these events to the IRB.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials,” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at:

https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control. In addition, there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs: the *Data and Safety Monitoring Committee* (DSMC) for Phase I and Phase II clinical trials, and the *Data and Safety Monitoring Board* (DSMB) for Phase III clinical trials. These committees report to the Center‟s Research Council and Institutional Review Board. During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

14.0 PROTECTION OF HUMAN SUBJECTS

Risks: The expected risks are minimal. The hyperspectral imaging system uses halogen light, which is also widely used as a commercial light source. The risk of drug side effects will be minimized by accurate selection of volunteers. Moreover, the experiments will take place in a controlled research setting (eg a hospital).,

Benefits: There is no benefit for the recruited healthy human volunteers upon participation to this study.

Toxicities/side effects: Participants will be made aware of potential side effects as explained in Section 8.0

Alternatives/options: Participants will be made aware that they can choose not to take part in this study or take part in another study if one is available, there are no standard alternatives/options as the population consists of healthy volunteers.

Financial costs/burdens: Participants will not be charged for participating, the non-investigational drugs will be provided free of charged, and participants will be offered a $50 gift card for participation at the end of the session.

Privacy and confidentiality: All the data will be confidential, maintained in a password protected electronic, secure and restricted departmental database and will comply with all HIPAA guidelines

Adverse event reporting: All adverse events will be reported as per section 14.2

Voluntary nature of the study: It will be made clear that participation is voluntary, and their employment or standing will not be impacted by their decision to participate or not.

14.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

14.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

As this is a minimal risk study, we will only report SAEs (including deaths) that are believed to be at least *possibly* related to the protocol intervention.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.
Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be

submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols: The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

15.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized, de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information, which will not include protected health information such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

16.2 Data Management

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

17.0 REFERENCES

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18.0 APPENDICES

Appendix 1. User Manual
Appendix 2. Non-Significant Risk Device Justification
Appendix 3: LUMC Protocol

Memorial Sloan Kettering Cancer Center
1275 York Avenue
New York, New York 10065