IIT2016-19-DASKIVICH-18F: High-Resolution, 18F-fluciclovine PET-MRI for Mapping Prostate Cancer in Patients Considering Focal High-Intensity Focused Ultrasound (HIFU) Therapy

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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 U.S. federal regulations and ICH guidelines.

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PI Signature: _____

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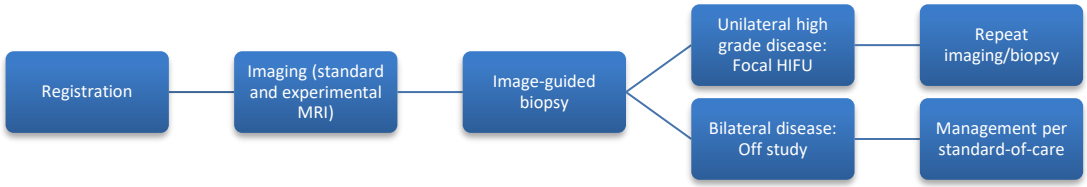
LIST OF ABBREVIATIONS

AE	Adverse Events
ADC	Apparent diffusion coefficient
AUC	Area under the curve
AS	Active Surveillance
DCE	Dynamic contrast enhanced
DWI	Diffusion-weighted imaging
EPI	Echo-planar imaging
HIFU	High-intensity focused ultrasound
hrMRI	High resolution MRI
mpMRI	Multiparametric MRI
MR/US	MRI-ultrasound
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PI-RAD	Prostate Imaging-Reporting and Data System
PSA	Prostate specific antigen
PSAM	Prostate specific membrane antigen
ROI	Region of interest
SAE	Serious Adverse Events
UTI	Urinary Tract Infection

STUDY SCHEMA



STUDY SUMMARY

Title	High-Resolution, 18F-fluciclovine PET-MRI for Mapping Prostate Cancer in Patients Considering Focal High-Intensity Focused Ultrasound (HIFU) Therapy
Short Title	High resolution PET-MRI before prostate cancer HIFU
Protocol Number	IIT2016-19-DASKIVICH-18F
Phase	Phase II
Methodology	Single arm, paired imaging
Study Duration	3 years
Study Center(s)	Cedars Sinai Medical Center
Objectives	To determine if enhanced prostate imaging using two novel imaging technologies (high resolution DWI and 18F-fluciclovine PET-MRI) will detect prostate cancers not seen on standard multiparametric prostate MRI in patients considered candidates for focal HIFU.
Number of Subjects	20 Study Subjects
Diagnosis and Main Inclusion Criteria	Diagnosis: Clinically localized, unilateral, high-grade prostate cancer OR at high risk for having unrecognized high grade Prostate Cancer Inclusion Criteria: • Biopsy consisting of ≥ 10 tissue cores sampled • PSA ≤20 ng/mL (within 3 months of consent) • cT1-cT2c • Either overall Gleason score ≥ 7 with Gleason grade 4 or 5 component localized to one lobe (i.e. right or left) OR overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core • Patient considering focal HIFU therapy
Study Imaging	18F-fluciclovine PET-MRI in combination with multiparametric prostate MRI using high resolution DWI
Control Imaging	Standard multiparametric prostate MRI
Reference standard	MRI-targeted prostate biopsies will serve as the reference standard and all lesions seen on any MRI protocol will be biopsied.
Statistical analysis	Our hypothesis is that 35% of biopsy-proven tumors will be detected on PET-hrMRI and not on standard MRI. If we assume that no biopsy proven tumors will only be detected on standard MRI, at alpha=0.05, n=20 provides a power of 80%.

1.0 STUDY ABSTRACT

The arrival of High-Intensity Focused Ultrasound (HIFU) technology along with advances in prostate imaging may make focal gland ablation feasible. While the mainstays of therapy for clinically localized prostate cancer, surgery and radiation therapy, induce significant morbidity such as urinary incontinence, erectile dysfunction, and bowel dysfunction due to bystander effects of whole-gland treatment, HIFU permits focal destruction of prostate cancers, which has the potential to minimize these morbidities and maximize quality of life. Advances in prostate MRI allow the majority of high grade cancers to be detected. Software platforms exist that enable real-time fusion of prostate MRI images with ultrasound, which allows for targeting of prostate lesions found on MRI during transrectal biopsy. The confluence of all of this technology—HIFU, multiparametric MRI (mpMRI), and MR/US-fusion targeting—creates the possibility of highly targeted focal ablation of prostate cancers. Nonrandomized clinical trials of hemigland and focal ablation with HIFU in Europe have shown promising trifecta rates—cancer control, potency, & continence—up to 1y post-treatment.

While early results of HIFU therapy for clinically localized prostate cancer are promising, the effectiveness of HIFU therapy will ultimately be limited by the accuracy of prostate cancer imaging. Because prostate cancer is often multifocal, identification of all clinically relevant prostate cancer lesions is critical to complete treatment of the disease, whether it is hemigland or true focal ablation. Modern mpMRI is unable to detect 20% of high-grade cancer and approximately 50% of low-grade cancers. To address this shortcoming, our team at Cedars-Sinai has developed high-resolution prostate MRI (hrMRI) technology that improves resolution 5-fold compared with standard multiparametric MRI. (1) High-resolution imaging has been shown to detect 60% of tumors not seen on standard MRI.(2) Pairing this technology with PET may allow highly specific targeting for focal therapy. Because the oncological effectiveness of focal therapy depends on robust targeting, PET-hrMRI could provide a significant advantage in cancer control outcomes for HIFU.

We herein propose a prospective trial to evaluate the effectiveness of 18F-fluciclovine PET-hrMRI versus standard mpMRI at identifying prostate cancer targets for HIFU therapy. Patients with clinically localized, unilateral high grade prostate cancer (Gleason score 7-10 prostate cancer localized to one lobe on prior biopsies) OR at high risk for having unrecognized high grade prostate cancer (overall Gleason score 6 with $\geq$ half of systematic biopsy cores positive and $\geq$ 50% of core involvement in at least one core), interested in HIFU would receive both a standard mpMRI and 18F-fluciclovine PET-hrMRI. They would then undergo a mapping biopsy using a standard sextant template plus MRI/US-fusion targeted biopsy of any suspicious lesion on mpMRI or PET-hrMRI. The primary endpoint would assess the number of biopsy-proven cancers that mpMRI would have missed compared with PET-hrMRI. Following our tumor mapping study, patients with high grade disease (i.e. Gleason grade 4 or 5) in one lobe undergo hemigland or focal HIFU of that lobe. At 6 months, patients would undergo repeat prostate biopsy to assess the negative biopsy rate in the treated region and absence of Gleason grade 4 or 5 in the untreated region as secondary endpoints.

2.0 BACKGROUND AND RATIONALE

2.1 Prostate Cancer: Current Standard of Care in Treatment

Prostate cancer is the most common non-cutaneous cancer and the second-leading cause of cancer mortality in American men, accounting for 25% (192,280) of new cancer diagnoses and 9% (27,360) of male cancer deaths(3). Clinically localized prostate cancer accounts for the vast majority of new cancer diagnoses, with an estimated 91% of new cases diagnosed at local or regional stages(3). Traditional treatment options for localized disease vary widely, from watchful waiting or active surveillance to aggressive treatment with surgery, radiation therapy, or brachytherapy. Active surveillance is considered the standard-of-care for low grade (e.g. Gleason score 3+3=6) prostate cancers and even some intermediate risk cancers. On active surveillance, patients with long life expectancy who develop a component of high Gleason grade cancer (i.e. Gleason grade 4 or 5) are recommended to have definitive local therapy such as prostatectomy or radiation. While aggressive therapies such as surgery and radiation do offer the opportunity for cure, they are fraught with side effects that can significantly affect quality of life, including erectile dysfunction, urinary incontinence, and bowel dysfunction(4-7). Even recent advances in robotic surgery and radiation techniques have not appeared to significantly reduce the long-term morbidities of definitive local therapy.

2.2 HIFU: Historical Background and FDA Approval

High-Intensity Focused Ultrasound (HIFU) is a noninvasive therapy that precisely delivers ablative ultrasonic energy to deep tissues through skin and mucosa, allowing for transrectal focal ablation of prostate cancers. While the mainstays of therapy for clinically localized prostate cancer induce significant morbidity such as urinary incontinence, erectile dysfunction, and bowel dysfunction due to bystander effects of whole-gland treatment, HIFU permits focal destruction of prostate cancers by ablating either half of the prostate gland or only the tumor itself; these approaches have the potential to minimize morbidities associated with whole-gland treatment and thereby maximize quality of life. HIFU treatment (primarily hemigland and whole-gland) has been used extensively over the last fifteen years in Europe, Canada, and Mexico, and there are numerous articles describing its safety and effectiveness for this application in the Urology literature.

While HIFU therapy has a long track record abroad, it has only recently been approved for prostate ablation in the US. In October 2015, the FDA gave de novo clearance to the Sonablate 450 HIFU platform (manufactured by SonaCare Medical) for the ablation of prostate tissue, making it the first to be approved for this indication in the US. In November 2015, the Ablatherm HIFU platform (manufactured by EDAP TM SA) was given 510(k) clearance for the same indication. While the approvals for these devices do not specifically mention application to prostate cancer, academic and industry leaders are hailing this technology as a major advance for focal prostate therapy, hinting that this technology can avoid the morbidities of surgery for prostate cancer. Local academic centers have already begun to use and market this technology.

2.3 HIFU: International Experience with Prostate Cancer Treatment

HIFU therapy has been a mainstay of prostate cancer care in Europe, Canada, and Mexico for the last fifteen years, and cancer control and side effect outcomes have been very promising. A review of the randomized clinical trials, meta-analyses, and systematic reviews reporting on efficacy and safety of HIFU as primary treatment was recently reported, though this review included a mixed population with regard to tumor mix and ablation zone (whole-gland and hemigland). 5-year disease free survival rates were 61–95%. Common complications associated with HIFU were urinary retention (<1–20%), UTI (2–48%), stress urinary incontinence of any degree (<1–34%), and erectile dysfunction (20–86%). Rare complications included recto-urethral fistula (<2%), bladder neck stenosis, urethral stricture, perineal pain, urinary obstruction, epididymitis, and prostatitis. The largest institutional series of hemigland HIFU for low- (25%) and intermediate-risk (75%) prostate cancers suggested even better results, with return of erectile function for penetrative sex in 95% of men, 90% pad-free and leak-free continent, and 89% had no histological evidence of cancer at 6 months. 89% of men reached the trifecta status of pad-free, leak-free continence, erections sufficient for intercourse, and cancer control at 12 months.(8) True focal therapy is in a nascent stage of development, but early results are similar to hemigland treatment. In a prospective study of 42 men with low- and intermediate-risk cancer at University College London, 95% (95% CI 83–99%) were cancer free on biopsy at 12 months and 84% (95% CI 66–95%) reached trifecta status.(9) These results, though admittedly in highly selected populations, are clear improvements on cancer control and quality of life outcomes in modern surgical and radiation cohorts.

2.4 MRI for Prostate Cancer Imaging

Multiparametric MRI (mpMRI) combining T2-weighted, diffusion-weighted, and dynamic contrast enhanced (DCE) images is quickly becoming part of the standard of care for detection and localization of prostate cancer.(10, 11) Prostate MRI has been shown to have high sensitivity and specificity for high-grade prostate cancers, with approximately 80% false negative rate for detection of Gleason 7 or higher tumors. The Prostate Imaging-Reporting and Data System (PI-RADS) scoring system is a widely accepted rating system for estimating risk of cancer, using a 1–5 scale to provide clinicians with an estimate for likelihood of cancer; this scale uses T2-weighted imaging, diffusion weighted imaging, dynamic contrast-enhancement, and MRI spectroscopy to inform this assessment. Some variations on this scale, such as the UCLA prostate MRI scoring system, give more weight to the diffusion-weighted imaging component, since it is the component providing the most predictive utility.

Diffusion-weighted imaging (DWI) is sensitive to the diffusion of water molecules interacting with surrounding macromolecules. DWI, which provides a quantitative biological parameter called apparent diffusion coefficient (ADC) value, is a robust MRI parameter for differentiating benign and malignant prostate tissue.(12, 13) In fact, the latest version of the Prostate Imaging-Reporting and Data System (PI-RADS) scoring system relies almost exclusively on DWI to identify tumors in the peripheral zone, which is where the vast majority of prostate cancers form. Findings on T2 images are not used to identify cancer, and DCE images are only used to differentiate between some PI-RADS 3 and 4 lesions. In a pilot study of prostate cancer AS, DW-MRI was useful for detecting progression of Gleason score based on changes in ADC value.(14) Tumor size is an important clinical criterion for defining low risk prostate cancer, and tumor size based on DWI has been shown to crudely predict low risk prostate cancer.(15) However,

conventional DWI using single-shot echo-planar imaging is unable to detect small tumors(16) or detect small changes in tumor size on serial imaging.

2.5 High-Resolution Prostate MRI (hrMRI)

Over the last several years, our group at Cedars-Sinai has developed technology to improve resolution of standard mpMRI, allowing for improved detection of smaller tumors. (1, 2) By using a three-dimensional (3D) high-resolution diffusion-weighted imaging sequence (HR-DWI), image quality is improved and confers a 5-fold improvement in resolution when compared to standard two-dimensional (2D) DWI (S-DWI). This novel 3D DWI technique has been developed by our team and can be applied on existing 1.5T or 3T MRI systems. S-DWI suffers from two important limitations. a) It uses single-shot echo-planar imaging (EPI) for data acquisition, which produces magnetic susceptibility induced streaking artifacts and geometric distortions so that round objects may appear oval. b) The relatively low signal-to-noise ratio and 2D image acquisition with S-DWI limit spatial resolution, which is defined by the minimum distance between two objects required to resolve them uniquely. Our hrMRI incorporating HR-DWI overcomes these limitations by using magnetization prepared, multi-shot, turbo-spin-echo acquisition, which improves signal-to-noise ratio (SNR), spatial resolution, and image quality, and eliminates geometric distortions and streaking artifacts associated with EPI.

In a prospective study assessing the performance of hrMRI in 17 prostate cancer patients on active surveillance, the technique was shown to detect tumors not seen on standard mpMRI. Standard mpMRI predicted biopsy results (AUC 0.72, Fisher's exact $p<0.001$), but high-resolution DWI sequences allowed MP-MRI to be more highly predictive of biopsy results (AUC 0.88, Fisher's exact $p<0.001$). hrMRI had a sensitivity of 95.7% and identified tumor in 22 of 23 zones proven to have cancer on biopsy. In contrast, standard mpMRI had a sensitivity of 60.9% and only identified 14 of 23 biopsy-positive zones ($p=0.004$). In all, hrMRI was shown to detect 60% of tumors not seen on standard MRI.

2.6 Fluciclovine and PET-MRI in Prostate Cancer

Positron emission tomography (PET) imaging has also been increasingly used for detection of occult distant metastases in patients with advanced prostate cancer using prostate-cancer-specific radiotracers (PSMA) or those that accumulate preferentially within prostate cancer tissue (11C choline, 11C acetate, and 18F fluciclovine). While PET technology is usually paired with CT imaging for 3D localization due to wide availability of CT technology, there have been efforts to pair PET technology with MRI to improve identification of lesions both within and outside of the prostate gland, given the advantages in spatial resolution of MRI over CT imaging. While mpMRI is a very sensitive imaging modality for identifying localized prostate cancers, its specificity is limited; co-localization of tumors identified on MRI with PET imaging may be able to improve specificity to account for this limitation.

18F-fluciclovine is a radiolabeled leucine (amino acid) analog that accumulates within prostate cancer, and early work has suggested that co-localization of this PET radiotracer with 3-D mpMRI imaging may enhance accuracy of localization of intraprostatic cancer lesions compared with mpMRI or PET/CT alone. In a study of 21 patients who underwent 18F-fluciclovine PET/CT and mpMRI prior to radical prostatectomy, combined 18F-

fluciclovine PET/CT and mpMRI imaging yielded a positive predictive value of 82% for tumor localization, which was significantly higher than that with either modality alone. This would suggest that pairing 18F-fluciclovine PET imaging with MRI directly may improve localization of cancers within the prostate for HIFU treatment planning. We hypothesize that further leveraging the sensitivity and spatial resolution of hrMRI with the specificity of PET imaging may further enhance performance in accurately identifying cancers within the prostate.

2.7 MR/US-Fusion for Targeting of Prostate Cancers

The advent of improved prostate imaging using multiparametric MRI and PET have dovetailed with advances in fusion software platforms that offer the ability to overlay static MRI images with real-time ultrasound images at the time of biopsy. This technology, called MR-US fusion, allows clinicians to target potential regions of interest in the prostate seen on mpMRI during an transrectal ultrasound-guided biopsy. Targeted MR-US fusion biopsies have been shown to significantly improve sensitivity and overall accuracy of biopsy over standard sextant biopsy by 24% and 14%, respectively. Most academic centers now offer MR-US fusion biopsies for patients with persistent rising PSA after negative standard biopsy and for surveillance biopsies while on active surveillance. MR-US fusion techniques are also being applied to focal ablation of prostate cancers with HIFU; both the Sonablate and Ablatheram HIFU plaforms have announced partnerships with MR-US fusion companies to provide targeting during tumor ablation with HIFU. However, despite these improvements, the accuracy of targeted biopsy and targeted focal therapy is necessarily limited by accuracy of the MRI imaging for detection and localization of lesions.

2.8 Combining MR/US-Fusion, hrMRI, and PET-MRI with HIFU for Focal Treatment of Prostate Cancer

Because the oncological effectiveness of HIFU depends on robust mapping and targeting of lesions within the prostate, improved detection of lesions using hrMRI and/or PET-MRI could provide a significant advantage in HIFU cancer control outcomes. Patients who are eligible for hemigland and focal HIFU absolutely depend on imaging for treatment planning; for example, in a patient with an index lesion of the right side of the prostate only, if imaging fails to detect a small focus of prostate cancer present on the left, hemigland HIFU (only treating the right side of the prostate) will not be effective at eradicating the entire bulk of his disease. It is even more important to accurately identify all prostate cancers when mapping for true focal therapy, since only identified lesions are ablated. We have previously shown that hrMRI detects up to 60% of tumors within the prostate not seen on mpMRI, and PET-MRI techniques may be able to improve the accuracy of this detection. Even if lesions that are ignored by mpMRI but detected on PET-hrMRI are indolent, long-term growth of these lesions may certainly affect cancer control outcomes over time and require costly and morbid retreatment. We believe that improved imaging at the outset of focal therapy would provide more comprehensive eradication of cancer burden from the start, resulting in improved long-term outcomes.

3.0 STUDY DESIGN:

3.1 Overview

This prospective trial will evaluate the effectiveness of 18F-fluciclovine PET-hrMRI versus standard mpMRI at identifying prostate cancer targets for HIFU therapy. Patients with clinically localized, Gleason score 7-10 prostate cancer localized to one lobe on prior biopsies or overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core, interested in HIFU would receive both a standard mpMRI and 18F-fluciclovine PET-hrMRI. They would then undergo a mapping biopsy using a standard sextant template plus MR/US-fusion targeted biopsy of any lesions with PI-RADS scores ≥3 on hrMRI or 18F-fluciclovine PET positivity. The primary endpoint would assess the number of biopsy-proven cancers that mpMRI would have missed compared with hrMRI and/or 18F-fluciclovine PET. Following our tumor mapping study, patients with high grade disease (i.e. Gleason grade 4 or 5) in one lobe undergo hemigland or focal HIFU of that lobe. At 6 months, patients would undergo repeat mpMRI and prostate biopsy (MR/US-fusion biopsy plus standard sextant biopsy) to assess the negative biopsy rate in the treated region and absence of Gleason grade 4 or 5 in the untreated region as secondary endpoints

3.2 Study Population

The study population for recruitment will be patients within the academic urology practice at Cedars-Sinai Medical Center. After initial visit, any patient with clinically localized prostate adenocarcinoma with Gleason score 7-10 prostate cancer localized to one lobe on prior biopsy desiring therapy with HIFU may be considered a potential study participant. Subjects with newly diagnosed disease or on active surveillance may be considered.

3.2.1 Inclusion Criteria

1. Biopsy consisting of ≥ 10 tissue cores sampled
2. PSA ≤20 ng/mL (within 3 months of consent)
3. cT1-cT2c
4. Either overall Gleason score ≥ 7 with Gleason grade 4 or 5 component localized to one lobe (i.e. right or left) OR overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core
5. Patient considering focal HIFU therapy

3.2.2 Exclusion criteria:

1. Previous local therapy for prostate cancer
2. Inability to receive PET tracer
3. Inability to receive MRI
4. Suggestion of extracapsular extension or seminal vesicle invasion on imaging, if imaging was completed per SOC prior to or during screening
5. Estimated creatinine clearance <45 mL/min (Cockcroft-Gault equation)
6. Any other condition which, in the investigator's option, may make the patient a poor candidate for participation in a clinical trial.

3.3 Study endpoints

Primary Endpoint: To determine the number of biopsy-proven cancers that standard imaging would have missed compared with PET-hrMRI on mapping MRI

Secondary Endpoint: Negative biopsy rate on standard 12-core biopsy 6 months following HIFU therapy.

Exploratory Endpoint: RNAseq transcriptome analysis of lesions that are positive on mapping biopsy.

3.4 Study Procedures

3.4.1 Screening/Baseline Procedures

Subjects will be identified by study investigators within the academic urology practice at Cedars-Sinai Medical Center during routine clinical practice. All study assessments for eligibility are performed as part of standard of care. Once a patient has been diagnosed, expressed interest in HIFU, and recommended study participation, they will be presented with the Informed Consent Form, including a description of the study purpose, risks, benefits and possible alternatives. The prospective participant will be given sufficient time to consider participation in the research. Patients will be asked to sign the study consent form after receiving a complete explanation of the study.

This study will enroll patients with clinically localized, Gleason score 7-10 prostate cancer localized to one lobe on prior biopsies or overall Gleason score 6 with ≥ half of systematic biopsy cores positive and ≥ 50% of core involvement in at least one core, interested in HIFU as primary treatment. Patients with low Gleason grade cancer (e.g. Gleason grade 3) on the contralateral lobe are allowed since the standard-of-care for such low grade disease is observation. Patients with very low risk disease and low-volume, low-risk disease are excluded since their preferred management is active surveillance. Patients will present with newly diagnosed disease or after a period of active surveillance. If there is suggestion of extracapsular disease or seminal vesicle involvement on MRI, these patients will be excluded. Metastatic workup with cross sectional imaging and/or bone scan will not be mandatory, since they are not indicated for low- and intermediate-risk prostate cancers according to AUA and NCCN guidelines.

Screening procedures include:

3.4.1.1 Informed Consent

Informed consent must be obtained prior to any protocol assessment or procedure which is not performed as part of local routine care. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). Signed and dated ICF and HIPAA for enrolled participants who are not subsequently screened or undergo study intervention will be maintained at the study site.

3.4.1.2 Medical history

Medical history (comorbidities) includes clinically significant diseases that are currently active or that were active, including past surgical history, medications, social history,

family history including history of prostate cancer, dates of previous prostate biopsies, prostate biopsy pathology results, PSA results, dates and results of previous prostate imaging

3.4.1.3 Reporting on Concomitant medication

Any current concomitant medications and treatments will be recorded

3.4.1.4 Demographics

Age, ethnicity/race

3.4.1.5 Review subject eligibility criteria

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion and none of the exclusion criteria.

3.4.1.6 Physical exam including vital signs, height, and weight

Physician directed physical exam. This may be collected within 90 days of screening.

3.4.1.7 Adverse event assessment

Adverse events will be assessed at imaging, post imaging (biopsy), HIFU, and HIFU follow up. See section 5.1 and 5.2 for Adverse Event and reporting. Only grade 3 and above imaging-related AEs will be captured and all SAEs following the receipt of fluciclovine F18.

3.4.2 Study Calendar

Procedure	**Screening**	**Imaging**	**Post-imaging[2]**	**Standard of Care (SOC) Treatment**	**Post SOC Treatment 6 months (+/- 1.5 months) following HIFU**
Informed Consent/Registration	X				
Demographics/Medical History	X				
Prior and Current Medication Review	X				
Vital Signs[5]	X				
Physical Exam[5]	X				
Symptoms Assessment	X				
Standard MRI		X (at least one day prior to targeted prostate biopsy)			X (at least one day prior to targeted prostate biopsy)
			X		X

Tissue collection[4]					
18-fluciclovine PET-hrMRI		X (at least one day prior to targeted prostate biopsy)			
Adverse Event Review[6]		X	X	X	X
Hemigland or Focal HIFU[1]				X (performed within 4 months after mapping and/or targeted prostate biopsy)	
Standard Sextant Mapping Biopsy			X		X
MR/US-fusion targeted biopsy			X[3]		X

1. Focal HIFU performed on study for patients with confirmed unilateral high grade prostate cancer.
2. End of study for bilateral Gleason ≥7 disease
3. Of any lesions with PI-RADS scores ≥3 on hr MRI or 18F-fluciclovine PET positivity
4. Tissue collection includes left over tissue from standard of care collection only.
5. Do not need to be repeated if obtained within 90 days of screening.
6. Only grade 3 and above imaging-related AEs will be captured and all SAEs following the receipt of fluciclovine F18.

Pre-HIFU Imaging Protocol for Tumor Mapping
Eligible participants will then undergo mapping MRI in advance of HIFU therapy using both standard mpMRI and PET-hrMRI. All imaging will be completed in one sitting. hrMRI increases the length of the MRI by approximately 5 minutes. PET-MRI sequences increased the length of mpMRI by 30 minutes. Scanning will be done on the Siemens Biograph mMR scanner at the Research Imaging Core facility in the Davis Building.

Subjects undergoing a PET-hrMRI will be screened using the standard clinical protocol to determine whether it is safe to administer contrast to the subject.

PET scans involve injection of a radioisotope. Subjects undergoing a contrast-enhanced MR-PET will be screened using the standard clinical protocol to determine whether it is safe to administer contrast to the subject. An IV line will be inserted, and the participant will receive 10 mCi ±20% 18F-fluciclovine injection diluted up to 10mL injected via the IV, as an IV bolus injection followed by 10mL flush with normal saline solution. The participant will then be positioned supine in the scanner and will be scanned in the area of the prostate. The research PET scan will be a dynamic list mode scan. Meaning the PET would start first, then 18F fluciclovine would be injected immediately after the scan is started. For the PET acquisition, participants will be imaged for approximately 30 minutes.

All MRI images will be read according to PI-RADS (version 2) by a dedicated GU radiologists who has experience reading over 500 prostate MRIs. All PET scans will be

read by nuclear medicine co-investigators on the study (DA, LT). All lesions with PI-RADS greater than or equal to 3 and all PET positive areas will be considered suspicious for cancer. A region of interest (ROI) application will be used. The circumference of a suspicious lesion will be drawn on each individual MRI slice. The lesion volume and average ADC will be calculated from the ROI's. The tumor volumes and ADCs will be provided by the radiologist. To prevent the hrMRI from influencing the review of the mpMRI, all mpMRI's will be reviewed first. The radiologist will always be blinded to previous pathology.

Mapping Biopsy Protocols
After the pre-HIFU imaging protocol for tumor mapping, all patients will undergo a transrectal ultrasound-guided targeted mapping biopsy. The biopsy will include a standard sextant template plus MR/US-fusion targeted biopsy of any lesions with PI-RADS scores ≥3 on hrMRI or 18F-fluciclovine PET positivity. These areas will be targeted using the UroNav targeting software platform. As an exploratory analysis, remnant formalin-fixed paraffin embedded tumor tissue will be requested for RNAseq transcriptome analysis of lesions that are positive on mapping biopsy.

Eligibility for HIFU
If subjects are found to have unilateral high grade disease (i.e. Gleason grade 4 or 5), they will be considered as a candidate for hemigland or focal HIFU therapy. Clinician judgment may be exercised in determining eligibility for HIFU, since established criteria based on volume and extent of disease do not exist. If patients have high grade disease in both lobes, they will not be eligible for HIFU therapy on this trial. Their data will be used to assess the primary endpoint but they will not be considered for secondary endpoints.

HIFU Therapy and Follow Up Schedule
Patients who are eligible for HIFU will receive hemigland or focal HIFU per standard-of-care. All subjects will receive repeat mpMRI and MR/US-guided biopsy of all positive sites + systematic 12-core prostate biopsy at 6 months (or as clinically indicated). As an exploratory analysis, remnant formalin-fixed paraffin embedded tumor tissue will be requested for RNAseq transcriptome analysis of lesions that are positive on biopsy.

3.5 Removal of Subjects from study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

3.5.1 Patient voluntarily withdraws (follow-up permitted);

3.5.2 Patient withdraws consent (discontinue all study procedures and follow-up)

3.5.3 Patient is unable to comply with protocol requirements;

3.5.4 Treating physician determines continuation on the study would not be in the patient's best interest;

3.5.5 Lost to follow-up. If a research subject cannot be located in order to obtaining data to inform the primary or secondary endpoint, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

4.0 Study Risks

All agents administered to patients and all invasive procedures used in this study are approved by the U.S. Food and Drug Administration. This study investigates a novel software-based MRI imaging protocol that improves image resolution, and it investigates the off-label use of F18 fluciclovine for prostate PET-MRI.

F18 fluciclovine is currently approved for PET-CT for men with suspected prostate cancer metastasis. MR/ultrasound fusion biopsies and HIFU for prostate ablation are also approved procedures that are being routine performed as standard-of-care. All invasive procedures will therefore be performed following standard informed consent.

Magnetic Resonance Imaging (MRI)
MRI imaging is among the least invasive of all imaging modalities. The U.S. Food and Drug Administration has labeled MR systems of up to 4.0 Tesla as having "non-significant risk" and currently there is no evidence that MR imaging causes any long-term or irreversible effects in human beings. However, there are certain risks, which are detailed below.

MRI imaging utilizes magnetic fields and radiofrequency fields, both of which can be harmful in certain situations. Magnetic fields can cause ferromagnetic implants or ferromagnetic foreign bodies, such as intracranial aneurysm clips, shrapnel, and intraocular metal chips to become dislodged and tear the surrounding soft tissue. Therefore, MRI imaging is contraindicated in persons with ferromagnetic implants or ferromagnetic foreign bodies. It is also contraindicated in persons with electrically, magnetically or mechanically activated implants because the magnetic field can cause these to function erratically. In addition, persons wearing metallic objects may be at danger for them becoming dangerous projectiles, due to them inadvertently becoming introduced into the magnetic field. All subjects will be prescreened carefully and all

scanners are used in accordance with guidelines set by the Bureau of Radiological Health.

Fluciclovine F18 (Axumin)
The recommended dose is 370 MBq (10 mCi) administered as an intravenous bolus injection. The (radiation absorbed) effective dose resulting from this dose of Axumin is 8 mSv. The clinical trial database for Axumin includes data from 877 subjects including 797 males diagnosed with prostate cancer. Most patients received a single administration of Axumin, a small number of subjects (n = 50) received up to five administrations of the drug. The mean administered activity was 370 MBq (range, 163 to 485 MBq). Adverse reactions were reported in ≤1% of subjects during clinical studies with Axumin. The most common adverse reactions were injection site pain, injection site erythema and dysgeusia.

Hypersensitivity to Medications - Occasionally, people have allergic reactions when taking any medication. Subjects may receive medications such as contrast. Hypersensitivity reactions may include symptoms such as shortness of breath, wheezing, flushing, nasal congestion and skin rash. In most cases, initial symptoms occur within minutes of drug administration and quickly reverse themselves or resolve with prompt medical treatment.

In general, allergic reactions to medicines are more likely to occur in people who have allergies to other drugs, foods, or things in the environment. Subjects will be asked about any pre-existing allergies before administering any medications during the study.

Incidental Findings
Only noted clinically significant incidental findings will be communicated to the subject, per CSMC IRB and Legal Department approved policy, as a result of agreeing to undergo a research MRI scan. No reports or images will be provided to subjects and their medical records. However, MRI mapping results will be provided to the treating physicians who will use this information for MR/ultrasound guided prostate biopsy.

5.0 ADVERSE EVENTS (AE)

5.1 Definitions

5.1.1 Adverse Event: An adverse event is any untoward medical occurrence in a patient receiving study intervention and which does not necessarily have a causal relationship with this intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or

disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

5.1.2 Serious Adverse Events (SAE): A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

- Results in death. If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- Is life-threatening.
  (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy Attribution categories are as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in section 1.4
- the drug package insert
- the current Investigator's Brochure

5.1.3 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, 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;

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known to an individual or group of individuals (including research subjects, research staff, or others not directly involved in the research).

5.2 Reporting Requirements

5.2.1 Reporting to the Institutional Review Board (IRB)

The IRB must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others."

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

5.2.2 Reporting to the FDA

The investigator or his designee must submit SAEs on FDA Form 3500A (MedWatch) according to the following reporting criteria:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions no later than 7 calendar days after initial receipt of the information.

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction no later than 15 calendar days after determining that the information qualifies for reporting.

5.2.3 Reporting to Blue Earth Diagnostics

In addition to reporting of SAEs to the responsible IRB/IEC and Health Authority, Principal Investigator or designee will document all SAEs that occur following receipt of fluciclovine Fl8 (whether or not related to study drug) to BED. Such SAEs must be reported within 24 hours of Principal Investigator or designee becoming aware of the event. All SAE information must be recorded and faxed or scanned and emailed to:

Blue Earth Diagnostics SAE E mail:	Drugsafety@pharsafer.com
Tel:	1-855-AXUMINI (1-855-298-6461)
Fax:	+44 (0) 1483 212178

Additional and further requested information (follow-up or corrections to the original case) will be detailed and faxed/emailed to the same address and must include the following minimum information: The name and contact information of the reporter, the name of the study drug(s), a description of the reported SAE, with the patient identified by one or more of the following (patient initials, patient number age, sex), an investigator assessment of study drug causality, and any additional data which would aid the review and causality assessment of the case including but not limited to the date of onset, severity, the time from administration of study drug(s) to start of the event, the duration and outcome of the event, any possible etiology for the event, and the final diagnosis or syndrome, if known.

6.0 Statistical Analysis

Primary Endpoint: To compare the number of biopsy-proven cancers that standard imaging would have missed compared with PET-hrMRI on mapping MRI (i.e. comparison of sensitivity of PET-hrMRI with mpMRI with biopsy-proven cancer as the gold standard).

Our preliminary data suggests that up to 60% of tumors invisible to standard mpMRI are detected on hrMRI. It is unclear how many additional lesions will be identified on fluciclovine PET-MRI. Since all areas of concern will be biopsied and only biopsy-proven tumors will be treated with HIFU, the morbidity of the surgical intervention is minimized and its potential to achieve cure is maximized.

Power Assessment: The power for the McNemar`s type test proposed by Durkalski et al. (2003) is evaluated based on four correlations: r1: between lesions evaluated by PET-hrMRI for the same patient, r2: between lesions evaluated by mpMRI for the same patient, r3: between evaluations PET-hrMRI and mpMRI for the same lesion and r4: between evaluations PET-hrMRI and mpMRI for the different lesions at the same patient. In this way, we define four scenarios of correlation among lesions: (a) no correlation (r1 = r2 = r4 = 0, r3 = 0.15), (b) low correlation (r1 = r2 = 0.1, r3 = 0.15, r4 = 0.015), (c) medium correlation (r1 = r2 = 0.4, r3 = 0.15, r4 = 0.06) and (d) high correlation (r1 = r2 = 0.8, r3 = 0.15, r4 = 0.12). In addition, the number of lesions for each patient is defined as equal to 1 - 2 on average from preliminary data.

The minimum sample size to reach 80% of power is 22 patients when each patient has exactly 1 lesion (total of 22 lesions); 19 patients when the average number of lesions is 1.35 (total of 26 lesions); and 17 patients when the average number of lesions is 2 (total of 34 lesions). Given that our estimated number of biopsy-proven lesions per patient will be 1–2 based on historical data, we will proceed with a sample size of 20 patients.

Statistical Analysis: Sensitivities will be compared using McNemar`s type test proposed by Durkalski et al. (2003) for cluster matched binary data. In addition, the 95% confidence interval for difference between sensitivities will be calculated as proposed by Yang et al. (2012).

Secondary Endpoints: Negative biopsy rate within treatment zones on standard 12-core biopsy 6 months following HIFU therapy; rate of high grade cancer in the untreated lobe.

Exploratory Endpoint: Formalin-fixed paraffin embedded biopsy tissue will be requested from a subset of patients for RNAseq transcriptome analysis. The number of cases analyzed will depend on availability of future funding. The subset of cases requested will depend on the exploratory object of the pilot study and may include discovery of signatures to predict presence of high grade cancer, unilateral disease or treatment success.

7.0 STUDY MANAGEMENT

Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause intervention delays after registration should be discussed with the Principal Investigator (PI). If a patient does not receive protocol intervention following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study team will track all subjects who sign consent on a subject screening/enrollment log using a unique screening ID (S001, S002, etc.). Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using only the three-digit numeric ID assigned at screening that follows the standard SOCCI format (001, 002, etc.).

A) Eligibility Verification

Prior to registration, all subjects must undergo eligibility verification by the SOCCICancer Clinical Trials Office (CCTO) . The following documents will be completed and provided for review:

- Registration form (or equivalent)
- Copy of applicable source documents
- Eligibility checklist (signed by investigator)
- Signed patient consent form and Subject's Bill of Rights

- HIPAA authorization form

B) Registration

After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Enter the patient in OnCore

Oversight by the principal investigator is required throughout the entire registration process

7.1 Data Management and Quality Control and Reporting

The data will be entered into a HIPAA-compliant database. The Study Staff will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

7.2 Data and Safety Monitoring

This trial is considered a minimal risk study, in which the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine examinations or tests required for the subject's disease.

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine Disease Research Group (DRG) meetings (or equivalent). In addition, the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct a focused internal monitoring visits and audits for data quality and protocol compliance.
QMC reports will then be forwarded to the SOCCI Data and Safety Monitoring (DSMC).

QMC will also conduct the following:
1. Central eligibility verification for all subjects enrolled as described in protocol section 3.2.
2. Central review of all eligibility waiver requests by a SOCCI Medical Reviewer to assess appropriateness and risk to ensure quality data and ensure subject safety protections for investigator-initiated research

Refer to the DSMC Charter for more details. For any protocol, QMC has the authority to request more frequent reviews or closer safety monitoring if it is deemed appropriate for any reason.

7.2.1 Safety Monitoring

Oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing

subject/study data. Adverse events and unanticipated problems are not expected, but if they occur they will be documented and reported according to CSMC IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly.

In addition, this protocol will utilize the SOCCI Data and Safety Monitoring Committee will provide another layer of data and safety oversight. Committee membership includes experts in the field of oncology, nursing, pharmacy, and biostatistics in reviewing the over data, safety, quality, and study integrity of SOCCI interventional IITs. DSMC membership and responsibilities are governed by the committee charter. The DSMC findings and recommendations will be reported in writing to the Principal Investigator. A summary letter will be forwarded by the Principal Investigator or his/her designee to the Cedars-Sinai Medical Center IRB. Refer to the DSMC Charter for details of the DSMC review.

7.3 Replacement of subjects

Any subject who signs consent but does not undergo study intervention (i.e. high-res imaging) will be replaced.

7.4 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, monitoring/auditing logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file per local guidelines.

7.5 Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and CSMC IRB, the study shall be conducted exactly as described in the approved protocol.

7.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator’s awareness of the event.

7.5.2 Protocol Exceptions and Eligibility Waivers

An exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy, Reporting Possible Unanticipated Problems

Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.

A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical and/or have the potential to affect the subject's safety and/or study integrity may not be implemented without prior approval from the SOCCI Cancer Center Trials Office (CCTO) Medical Director and IRB. The PI or her/his designee is responsible for submitting a protocol exception and its supporting documents to the SOCCI CCTO Medical Director for review.

Study team should refer to the IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement guidelines to determine which deviations and exception requests require prior approval from the SOCCI CCTO Medical Director. Once approved, the deviation or exception request must be submitted to the IRB for review and approval prior to implementation.

Special considerations for Eligibility Waivers (EW)
In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be forwarded to the SOCCI CCTO Medical Director for assessment **prior** to submission to the IRB for approval.

The CCTO Medical Director will review the case and contact the investigator if additional information is needed or further discussion is warranted. The CCTO Medical Director will provide a written assessment/recommended course of action. The CCTO Medical Director's assessment must be uploaded into CS-IRB with the waiver request for IRB review and consideration. The CCTO Medical Director may recommend future protocol changes.

Eligibility Waiver Submission Process
The PI and/or treating physician should provide written request for waiver which includes case history and justification for prospective deviation from the study design to the SOCCI CCTO Medical Director. "IIT Monitoring – Eligibility Waivers and Exception Requests (EW/ER) Form" must be completed, along with any applicable supporting documents, must be emailed to QMC (GroupSOCCICROQMC@cshs.org) to request an eligibility exception request from the CCTO Medical Director. This is only a requirement for studies with DSM classification of moderate or high. An assessment from the CCTO Medical Director or designee must be done prior to submission to the IRB for review.

7.5.3 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety. Such planned deviations that do meet this

definition and do not affect the subject's safety should be noted in the subject's research record or deviation log as described in the SOCCI Clinical Research Office's Working Instruction 11: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI Clinical Research Office's Working Instruction 11: *Deviation and Noncompliance Reporting*. In this case, a Protocol Deviation report must be submitted in Webridge, per IRB policy, *Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement*. All submissions should include a description of the plan to avoid similar deviations or exceptions in the future.

7.5.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

7.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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9.0 SUMMARY OF CHANGES

Protocol Version 2, dated 02 JUL 2018, amends Protocol Version 1 IRB approval on 07 DEC 2017.

Amendment 1: See changes below:

Section 3.4 (Study Procedrues)

- Clarification that physician directed physical exam may be collected within 90 days of screening.
- Clarification to adverse event assessment: "Only grade 2 and above imaging-related AEs will be captured and all SAEs following the receipt of fluciclovine F18."
- Clarification that MRI images will be read by one GU radiologist, not two.

Section 5.0 (Adverse Events)

- Reporting procedures for "Serious Adverse Events" included.

Section 5.2 (Reporting Requirements)

- Addition of "Reporting to the FDA section" describing the procedures for reporting SAEs to the FDA.
- Addition of "Reporting to Blue Earth Diagnostics" describing the procedures for reporting SAEs to Blue Earth Diagnostics.

Protocol Version 2.1, dated 13 NOV 2018, amends Protocol Version 2 IRB approval on 23 JUL 2018.

Amendment 2: See changes below:

Section 3.2.2 (Exclusion Criteria) #4

- Clarification of exclusion #4 "suggestion of extracapsular extension or seminal vesicle invasion on imaging, if imaging was completed per SOC prior to or during screening". Exclusion #4 would only apply if the subject had imaging performed as part of SOC. Study calendar confirm that imaging is not required as part of screening and therefore this criterion does not apply to patients who do not receive SOC imaging prior to or during the screening period.

Protocol Version 2.2, dated 06 FEB 2019, amends Protocol Version 2.1 IRB approval on 19 NOV 2018.

Amendment 3: See changes below:

Section 3.2.1 (Inclusion Criteria) #2

- Clarification of inclusion #1 "PSA <20 ng/mL (within 3 months of consent)". Timeframe for the PSA result clarified to be within 3 months of consent.

Protocol Version 2.3, dated 19 MAR 2019, amends Protocol Version 2.2 IRB approval on 22 APR 2019.

Amendment 4: See changes below:

Section 3.4.2 (Pre-HIFU Imaging Protocol for Tumor Mapping)

- Clarification in regard to 18F fluciclovine injection and PET scan time. The research PET scan will be a dynamic list mode scan. Meaning the PET would start first, then 18F fluciclovine would be injected immediately after the scan is started.

Protocol Version 2.4, dated 17 June 2019, amends Protocol Version 2.3 IRB approval on XX XXX XXXX

Amendment 5: See changes below:

Section 7.2 Data and Safety Monitoring

- Clarification of QMC monitoring role.

Section 7.2.1 Safety Monitoring

- Clarification of site monitoring.

Section 7.5.2 Protocol Exceptions and Eligibility Waivers

- Clarification of protocol exception and eligibility waiver process.