Official title: Initial evaluation of role of early interim ^{18}F-FLT PET/CT for outcome prediction in pancreatic adenocarcinoma

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PROTOCOL Version 7

PROTOCOL TITLE

Initial evaluation of role of early interim ^{18}F-FLT PET/CT for outcome prediction in pancreatic adenocarcinoma

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Study Drug: 3'-deoxy-3'-[18F]-fluorothymidine

IND Number: **133348**

IND Holder Name: Neil Rofsky, MD.

Funding Source: Shelby Pancreatic Cancer Research Program

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Signature Page

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

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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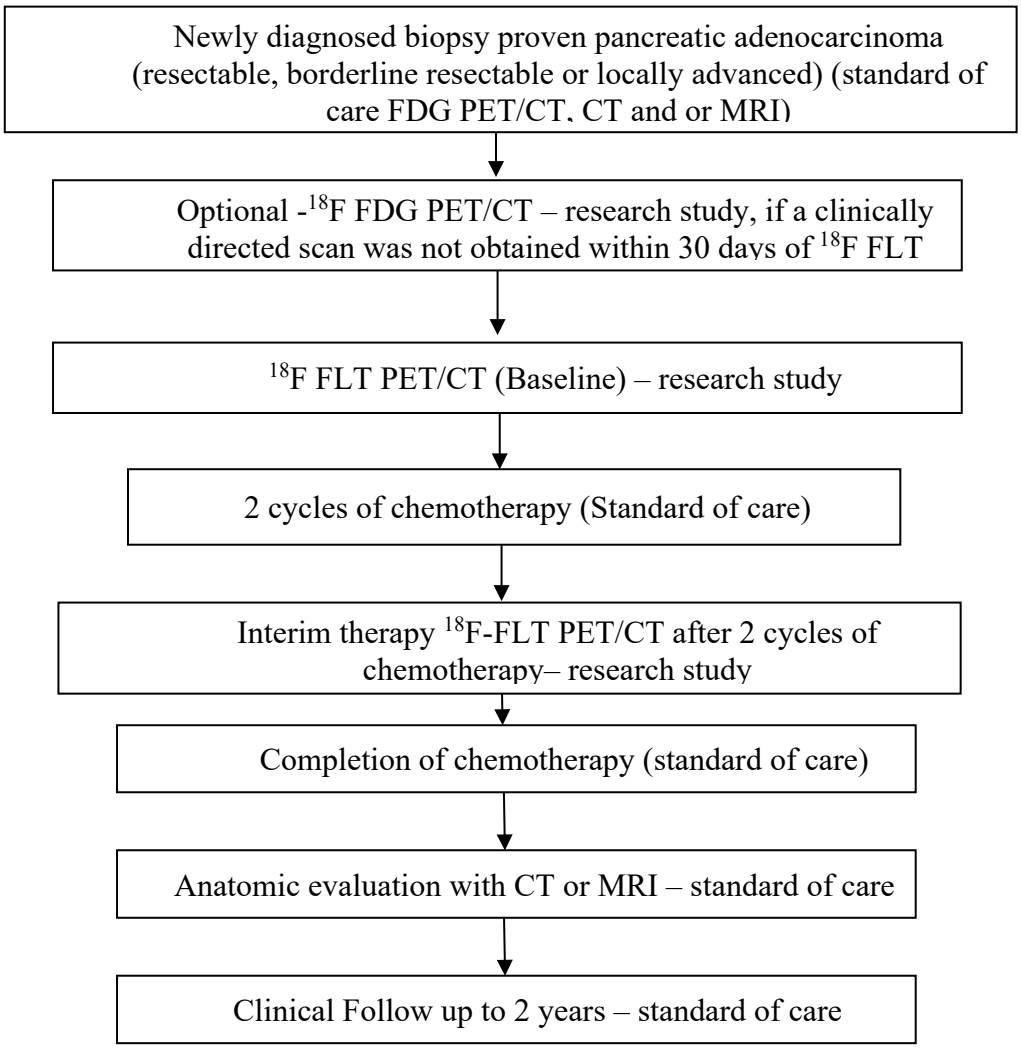
LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT`	Disease Oriented Team
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute

ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA

The schema should represent your study design, along with corresponding descriptive text, as applicable.



STUDY SUMMARY

Title	**Initial evaluation of role of early interim ^{18}F-FLT PET/CT for outcome prediction in pancreatic adenocarcinoma**
Short Title	FLT PET/CT and Pancreatic cancer early therapy assessment
Protocol Number	Version 7
Phase	Clinical study phase (e.g., Phase II)
Methodology	Prospective cohort study
Study Duration	2 years
Study Center(s)	UT Southwestern Medical Center - Single-center
Objectives	• To assess if percentage change in ^{18}F-FLT PET/CT quantitative parameters (SUV max, or SUV peak or proliferative tumor volume) after 2 cycles of neoadjuvant chemotherapy can predict overall survival at 1 and 2 years and progression free survival at 6 months and 1 year in patients with resectable, borderline resectable or locally advanced pancreatic adenocarcinoma.
Number of Subjects	20 patients with pancreatic adenocarcinoma

Diagnosis and Main Inclusion and exclusion Criteria	• Patients must be over 18 years old and capable and willing to provide informed consent
	• Patients of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to PET/CT imaging per institution's standard of care
	• Medically stable as judged by patient's physician
	• Patients must have an ECOG performance status of 0-3 (restricted to ECOG PS 0-2 if age >70 years)
	• Patients with known allergic or hypersensitivity reactions to previously administered radiopharmaceuticals of similar chemical or biologic composition to FLT are not eligible
	• Patient must NOT be breast-feeding
	• Histologically confirmed resectable, borderline resectable or locally advanced pancreatic adenocarcinoma
	  • Patient have measurable disease (by RECIST 1.1 criteria)
	• Patients with a history of prior therapy for pancreatic adenocarcinoma are NOT eligible
	  • Patient must not weigh more than the maximum weight limit for the table for the PET/CT scanner (>200kg or 440lbs) .
	• Patient must be able to lie still for a 20 to 30 minutes for whole body PET/CT scan

Study Product(s), Dose, Route, Regimen	Fluorothymidine is an analog of the nucleoside thymidine (deoxythymidine) but the 3'-F atom prevents FLT from following the full biochemical pathway of thymidine. FLT is transported from the blood into cells by active transport; it does not freely diffuse across the cell membrane. Once in the cell, FLT is a substrate for thymidine kinase I (TK1) and is phosphorylated but is not incorporated into DNA. 5mCi of FLT (+/- 20%) will be given intravenously.
Duration of administration	IV push over one to two minutes
Reference therapy	Not applicable

Statistical Methodology	The difference in SUVmax, SUVpeak and proliferative tumor volume between baseline and post 2 cycles of chemotherapy will be correlated with overall survival at 1 and 2 years (primary clinical outcome endpoint) and progression free survival at 6 months and at 1 year (secondary clinical outcome endpoint) of patients with resectable, borderline resectable or locally advanced pancreatic adenocarcinoma using univariate and multiple cox regression model. Patient demographic information and tumor and treatment characteristics such as sex, race, tumor grade, cancer stage, last treatment modality, will also be included. P value less than 0.05 will be considered as statistical significant. Areas under the ROC curve (AUC) and corresponding 95% confidence interval will be calculated for all models. Leave one out cross validation will be applied to avoid over-fit.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Pancreatic cancer is the fourth most lethal malignancy overall, with a projected death toll of more than 40,000 for 2016 in the US[1]. Pancreatic adenocarcinoma is usually locally advanced and / or metastatic at the time of diagnosis, preventing surgical resection in the majority of cases[2]. Initial treatment strategies for resectable, borderline resectable or locally advanced pancreatic adenocarcinoma includes chemotherapy and chemoradiation (in selected patients). The main therapeutic goal is to reduce disease burden to allow surgical resection, which is the only curative treatment for pancreatic adenocarcinoma to date. After initial treatment, response is revaluated by anatomical imaging, usually by a dedicated contrast enhanced CT, which is preferred, or alternatively MRI. However, objective evaluation of response in pancreatic cancer is often difficult. CT and MRI have some significant limitations, such as inability to clearly outline tumor borders due to the infiltrative nature of pancreatic adenocarcinomas, and post-treatment imaging changes that can simulate tumor. Additionally, it is an anatomic method only that relies on relatively slow macroscopic tumor changes without information regarding tumor metabolism.

2-Deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}F-FDG) PET/CT, which is a marker of glucose metabolism, is an alternative imaging method, and multiple studies have shown an overall sensitivity of 73 to 94% for detection of pancreatic adenocarcinoma, while specificity ranges from 60 to 89%. The specificity is reduced because ^{18}F-FDG PET/CT is a non-specific tracer that also accumulates in some benign conditions with increased glucose metabolism (such as inflammation). Moreover, the rate of false negatives is also

increased in this population because 20 to 30% of patients with pancreatic adenocarcinoma have hyperglycemia, which may significantly decrease the amount of FDG uptake[3-13]. For these reasons, more accurate novel PET tracers are expected to have a significant clinical impact.

1.2 Study Agent(s) Background and Associated Known Toxicities

The pharmacology of 3'-deoxy-3''[^{18}F]-fluorothymidine (FLT) is based on its action as an inhibitor of DNA synthesis. Intracellular metabolism of FLT produces FLT-phosphates but these nucleotides inhibit endogenous DNA polymerases because they lack a 3'-hydroxyl substituent. This results in premature chain termination of DNA synthesis[14].

In a study performed at the University of Washington, Turcotte and colleagues assessed the toxicity of ^{18}F-FLT in twenty patients with proven or suspected diagnosis of non-small cell lung cancer[15]. All patients gave written informed consent to the ^{18}F-FLT injection, and subsequent PET imaging and blood draws. Blood samples were collected for each patient at multiple times before and after ^{18}F-FLT. These samples were assayed for comprehensive metabolic panel, total bilirubin, and complete blood and platelet counts. In addition, a standard neurological examination by a qualified physician was performed for each patient before and immediately after ^{18}F-FLT. All ^{18}F-FLT doses were calculated based on patient weight (2.59 MBq/kg = 0.07 mCi/kg) with a maximal dose of 185 MBq (5.0 mCi). Starting with the ^{18}F-FLT injection, dynamic PET images were acquired for 90 or 120 minutes. By placing a region-of-interest in the center of the left ventricular chamber, blood time activity curves were generated for each patient from the dynamic PET data and then extrapolated to 720 minutes. This provided a measure of the area under the ^{18}F-FLT concentration curve for 12 hours (AUC_{12}). A separate estimation of the AUC_{12} was also obtained from sequential blood samples collected during PET data acquisition. No side effects were reported by patients or observed. No change was observed in the neurological status of patients. A neurological examination was performed by an experienced neurologist prior to ^{18}F-FLT administration, the day after ^{18}F-FLT administration, and at four weeks post ^{18}F-FLT administration. Only albumin, red blood cell count, hemoglobin, and hematocrit show a statistically significant decrease over time. These changes were attributed to IV hydration during PET imaging and to subsequent blood loss at surgery. The AUC_{12} values estimated from imaging data are not significantly different from those found from serial measures of ^{18}F-FLT blood concentrations (P = 0.66). No significant neurologic sequelae have been attributed to ^{18}F-FLT use in pet imaging to date. As a result, peripheral neuropathy, which had been listed as a possible risk based upon observations at significantly higher doses in early therapeutic HIV studies, is no longer considered a risk of ^{18}F-FLT use in a micro-dose imaging setting. Screening for peripheral neuropathy is not justified based upon the available evidence in multiple ^{18}F-FLT imaging trials.

In another study, 12 patients with brain tumors were enrolled[16]. Overall, 2 of the 12 subjects receiving ^{18}F-FLT experienced an elevation in BP from baseline to two hours post infusion: Subjects 1 (119/56 – 133/66) and 4 (120/78 – 163/74). In Subject 4, abnormal BP was attributed to discomfort from the head immobilization device. There were no clinically relevant events reported. All subjects performed consistently on the pre- and post- neurological exams and there were no changes in status. Four of these analytes demonstrated statistically significant changes on one-way ANOVA: potassium, carbon dioxide, total protein, and albumin. Some of the other values were above or below normal, but no pattern was seen except that many were lower on the day of the study. These decreases are attributed to two main factors. Normal saline infusion, which expands blood volume, and arterial blood sampling for kinetic analysis are performed during the procedure, both of which will cause a general lowering of the concentration of blood components. The subsequent recovery of these values to baseline is consistent with this explanation and consistent with the results obtained by Turcotte.

As discussed above, the mechanism of action of FLT's toxicity at therapeutic dosing levels is based on inhibition of DNA synthesis. Total exposure to the radiolabeled agent for PET imaging, will be several thousand times lower than the exposure at which toxicity has been observed in humans. Nevertheless, as with all investigational drugs, patients receiving ^{18}F-FLT should be observed for adverse events, and promptly treated should any adverse effects occur.

1.3 Other Agents

Not applicable.

1.4 Rationale

The thymidine analog 3'-deoxy-3''[^{18}F]-fluorothymidine (FLT) is a proliferation marker, which has the potential to perform better in patients with pancreatic adenocarcinoma[14].

Interim studies (usually after 2 cycles of chemotherapy) are commonly used for early restaging and to better tailor further management, offering more timely evidence to support changing or maintaining therapies, when compared to conventional imaging studies. It also has an important role in prognostication. Such study strategies have been extensively explored for breast cancer, and at least three different studies showed significant correlation between findings in early ^{18}F-FLT PET/CT and patients' response to chemotherapy, giving the possibility of change in chemotherapy regimens in non-responder patients[17-19].

The increased specificity of ^{18}F-FLT PET/CT has an enormous advantage over ^{18}F-FDG PET/CT as an early assessment study, especially with radiation therapy. ^{18}F-FDG PET/CT is known to suffer from an increased rate of false positives due to non-specific uptake in post-therapy inflammatory changes during treatment caused by macrophage / monocyte infiltration[20]. ^{18}F-FLT PET/CT has the potential to overcome this imitation as a more specific tracer for tumor proliferation.

1.5 Correlative Studies

Few studies have explored the role of ^{18}F-FLT PET/CT in pancreatic cancer. One study, which enrolled 31 patients undergoing resection, demonstrated a lower false-positive rate compared to ^{18}F-FDG PET/CT[21]. A second study reported that ^{18}F-FLT PET/CT was detected exclusively in malignant tumors, with a specificity of 100% for detection of pancreatic adenocarcinoma[22]. A more recent study evaluated the role of FLT PET/CT using a temporal-intensity information-based voxel-clustering approach termed kinetic spatial filtering (FLT PET/CTKSF) for early prediction of response and survival outcomes in locally advanced and metastatic pancreatic cancer patients receiving gemcitabine-based chemotherapy. The authors found that FLT PET/CT detected changes in proliferation, with early increase in SUVmax predicting progressive disease with a high specificity and PPV[23].

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

a. To assess if percentage change in ^{18}FFLT PET/CT quantitative parameters (SUV max, or SUV peak or proliferative tumor volume) after 2 cycles of chemotherapy can predict overall survival at 1 and 2 years in patients with resectable, borderline resectable or locally advanced pancreatic adenocarcinoma.

2.2 Secondary Objectives

b. To assess if percentage change in ^{18}FFLT PET/CT quantitative parameters (SUV max, or SUV peak or proliferative tumor volume) after 2 cycles of chemotherapy can predict progression free survival at 6 months and 1 year in patients with resectable, borderline resectable or locally advanced pancreatic adenocarcinoma.

2.3 Exploratory Objectives

None

2.4 Endpoints

Primary endpoint is to determine that a positive response (decrease on quantitative parameters) at an interim ^{18}F FLT PET/CT (performed after 2 cycles of chemotherapy) is related to longer progression free survival and overall survival.

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

a. Patients with histologically confirmed pancreatic adenocarcinoma (resectable, borderline resectable or locally advanced disease at presentation) are eligible for the study.

b. Patients should not have any type of curative or palliative therapy for pancreatic adenocarcinoma before enrolling in the study and should be candidates for induction chemotherapy.

c. Patients must be over 18 years old and capable and willing to provide informed consent.

d. Patients must have measurable disease (by RECIST 1.1 criteria)

e. Patients must have an ECOG performance status of 0-3 (restricted to ECOG PS 0-2 if age >70 years).

f. Patients of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to the FLT PET/CT and the optional FDG PET/CT imaging per institution's standard of care; A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria;

    i. Has not undergone a hysterectomy or bilateral oophorectomy; or
    ii. Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

g. Medically stable as judged by patient's physician.

h. Patients with known allergic or hypersensitivity reactions to previously administered radiopharmaceuticals of similar chemical or biologic composition to FLT or FDG are NOT eligible.

i. Ability to understand and the willingness to sign a written informed consent.

j. Patient must be able to lie still for a 20 to 30 minute PET/CT scan.

3.2 Exclusion Criteria

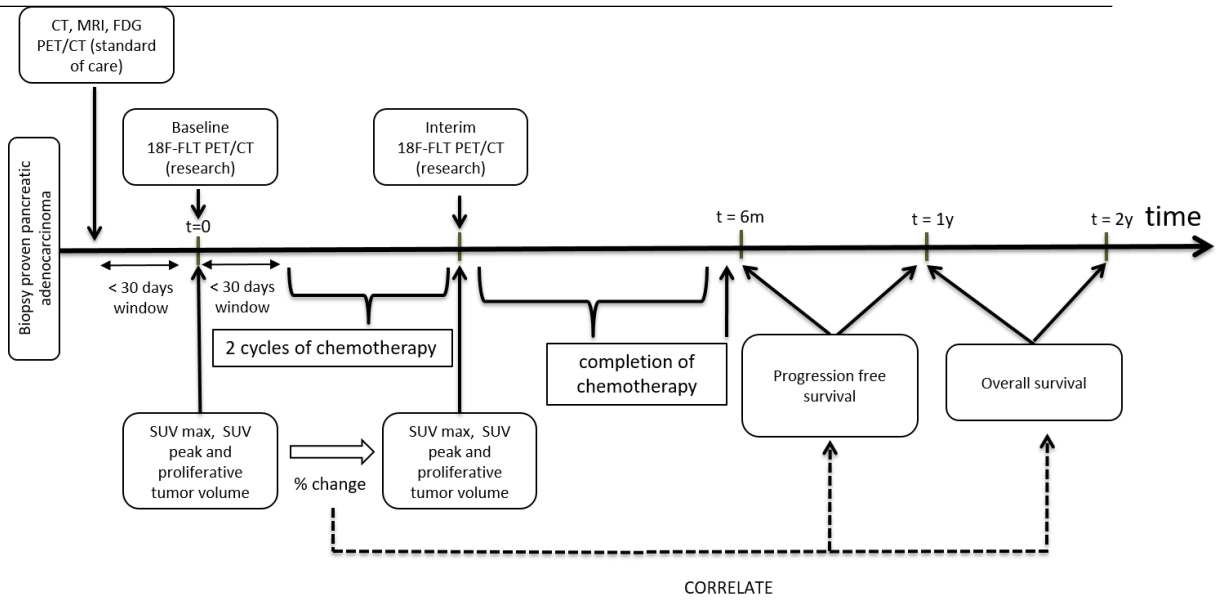
a. Subjects who had prior chemotherapy or radiotherapy for pancreatic adenocarcinoma cannot participate in the study.

b. Patient must NOT be pregnant or breast-feeding.

c. Patients have no clinical evidence of distant metastatic disease

d. Patients must not weigh more than the maximum weight limit for the table for the PET/CT scanner where the study is being performed.(>200kg or 440lbs)

4.0 STUDY PLAN



N.B: FDG PET/CT can be performed before or after baseline FLT, but must be within 30days of baseline FLT PET/CT.

The experimental ^{18}F-FLT-PET/CT is required to be completed before initiation of chemotherapy. Labs and correlative radiology, as directed per clinical care, are required within 30 days prior to ^{18}F-FLT-PET/CT; and optional ^{18}F-FDG-PET/CT within 30 days of the ^{18}F-FLT-PET/CT. Follow-up will comprise 24 months of standard practice treatment and follow up.

Visit 1: Patients will have at least one visit with investigator (or investigator designee) prior to the study to review clinical history and prior treatment of pancreatic adenocarcinoma, and to explain the study. Correlative radiology studies including CT, MRI and/or^{18}F FDG-PET/CT as per institutional routine clinical care, and any clinically-directed laboratory tests performed as part of staging. All clinical care tests must be performed within 30 days of the ^{18}F FLT-PET/CT.The following additional patient data will be obtained: histological diagnosis of primary and/or metastatic disease, date of diagnosis of primary and no evidence of metastatic disease, gender, height, weight (for BMI), ECOG score and confirmation of absence of prior treatment.

Visit 2(optional): The ^{18}F-FDG-PET/CT may be done as a research scan if patients agrees to that, if the patient is unable to obtain a clinically-directed ^{18}F-FDG-PET/CT as part of their clinical care or within 30 days of ^{18}F FLT-PET/CT, before or after the baseline FLT. The research ^{18}F-FDG-PET/CT, in this instance, will be identical in procedure to the institution's clinical ^{18}F-FDG-PET/CT. The blood glucose level will be < 200 mg/dl, before ^{18}F-FDG injection, which is institutional standard clinical protocol.

Visit 3: Day of ^{18}F-FLT-PET/CT: The patient will have an intravenous line placed in the hand or arm, ^{18}F-FLT-PET/CT will be given by 1-2 minute IV push, and the dose administered will be approximately 5 mCi (+/- 20% dose). After approximately 60 +/- 10 minutes of uptake time, the patient will be positioned supine in the PET/CT scanner for standard whole body PET/CT scan from the skull base to mid-thigh. This scan will take approximately 20-30 min. The window from FLT PET/CT baseline study to initiation of chemotherapy should be no more than 30 days.

Visit 4: Day of Interim ^{18}F-FLT-PET/CT: The interim ^{18}F FLT-PET/CT will be performed after the 2nd cycle of chemotherapy regimen, but before the commencement of 3rd cycle. The second ^{18}F-FLT-PET/CT study must be performed on the same scanner as the first ^{18}F FLT-PET/CT and the imaging protocol described in Visit 3 should be closely followed.

4.1 Study duration:

Clinical Follow Up: Standard of care clinical follow-up data will be collected up to 2 years following the end of chemotherapy.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 60 days prior to registration unless otherwise stated. The screening procedures include:

Informed Consent

Informed consent will be obtained from each research participant by the investigator or the study coordinator. No participant will be allowed to participate without a signed, IRB-approved, consent form.

Medical history

Review of complete medical and surgical history available in the electronic medical system at UT Southwestern Medical Center

Demographics: Age, gender, race, ethnicity

Review subject eligibility criteria

Review previous and concomitant medications

Available in the electronic medical system at UT Southwestern

Review of Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

Performance status

Review of ECOG Performance status evaluated prior to study entry.

Serum chemistries

Review of metabolic panel (CMP) to include (if available): albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.. Only labs ordered as standard of care and available in EMR (EPIC) at time of screening will be reviewed, new labs will not be ordered for research.

Pregnancy test (for females of child bearing potential)

See section 3.1.e. for definition.

5.2 Time and Events Table

SAMPLE	Visit 1: screening	Visit 2(optional): ^{18}F FDG PET/CT staging (if needed for research)	Visit 3: ^{18}F FLT PET/CT	Visit 4: Interim ^{18}F FLT PET/CT	Follow-up
Informed Consent	X				
Demographics	X				
Clinical history	X				
Height/weight	X	X	X	X	
Physical exam	X				
Survival/patient status					X
Review biopsy records	X				
^{18}F FLT PET/CT			X	X	
^{18}F FDG PET/CT (optional)		X			
Other radiologic studies (CT or MRI)	X				X
Pre-scan pregnancy test (if needed)		X	X	X	
Adverse event evaluation			X	X	

5.3 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or 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:

- Subject withdraws consent (termination of treatment and follow-up);
- Subject is unable to comply with protocol requirements;
- The researchers believe that participation in the research is no longer safe for the subject;
- Subject experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the subject's best interest;
- Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.4 Safety

As with all PET imaging agents, 3'-deoxy-3'-[18F]-fluorothymidine is a radiopharmaceutical that decays with positron emission. As such, it poses an intrinsic radiation exposure risk. However, this risk is felt to be extremely small, at the doses administered in this study. The organ and total body doses associated with FLT PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures.

The radiation absorbed effective dose equivalent to the whole body from intravenously injected ^{18}F-FLT is estimated to be 0.028±0.012 mSv/MBq. The total body doses associated with ^{18}F-FLT PET imaging are comparable to or lower than those associated with other widely used clinical nuclear medicine procedures and are well below the maximum suggested for individual study and annual total body dose of 30 and 50 mGy, respectively, suggested for investigational radiopharmaceuticals by the FDA.

The usual risks of PET studies include those due to IV line. The IV line risks are bleeding or a possible hematoma at the sight of injection. A physician will be available to document the adequacy of the venous line and provide assistance in case of inadvertent tracer extravasations or hematoma formation.

All adverse events occurring within a 24-hour period post-FLT infusion will be recorded. The adverse events to be specifically monitored during the infusion include localized discomfort at the IV injection site, pain, respiratory difficulties, flushing, dizziness, pruritus/rash, and any other symptoms that could be secondary to an anaphylactic reaction. The subject will be instructed to report any subjective symptoms or sensory changes noted.

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[24]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

This evaluation will be done at the CT or MRI by the end of chemotherapy and in follow up CT or MRI, performed as standard of care (up to 2 years). This information will be used for assessment of progression free survival at 6 months and at 1 year.

6.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and

should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI: Standard of care spiral CT will be performed with intravenous contrast (whenever possible) using a 5 mm contiguous reconstruction algorithm. MRI of the abdomen will be performed with intravenous contrast (also whenever possible) with multiple T1 and T2 weighted multiplanar sequences and volumetric dynamic post contrast images.

6.4 Response Criteria

6.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subjects best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.4.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.5 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (**http://ctep.cancer.gov/reporting/ctc.html**) and modified criteria for hematologic adverse events.

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who

will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

Definition

Adverse Events will be reported as indicated by the appropriate following table (see below).

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

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild

- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; Likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

All serious adverse events occurring within a 24-hour period post-FLT infusion will be recorded.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets each of the following criteria:

- Unexpected (in terms of nature, severity or frequency) AND
- Definitely or probably related to participation in the research AND
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

Reporting

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

7.2.3.1 UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. (See Appendix IV of the SCCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).

All serious adverse events which occur on research subjects on protocols for which the SCCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

Telephone reports to: (Investigator/study team: Dr. Pinho, Telephone: 214-648-5489)
Written reports to: (Investigator/study team: Dr. Pinho, Telephone: 214-648-5489, Fax: 214-648-7352, email: Daniella.Pinho@Utsouthwestern.edu) UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

SAEs

Serious adverse events (SAEs) for studies where Simmons Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is the DSMC of record, requires reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 48 hours of PI awareness of the event (life threatening or fatal events experienced by subjects Steps to Determine If an Adverse Event Requires Expedited Reporting

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.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

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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 the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

8.0 DRUG INFORMATION

3'-deoxy-3'-[^{18}F]-fluorothymidine

Other names for the drug(s): ^{18}F FLT

Classification - type of agent: Radiopharmaceutical

Mode of action: Fluorothymidine is an analog of the nucleoside thymidine (deoxythymidine) but the 3'-F atom prevents FLT from following the full biochemical pathway of thymidine. Once in the cell, FLT is a substrate for thymidine kinase I (TK1) and is phosphorylated but is not incorporated into DNA.

Protocol dose: 5 mCi (+/- 20%)

Preparation: Provided as unit dose by the UTSW cyclotron facility to inject into patients. FLT is administered to subjects by intravenous injection of ≤ 10 mL. The drug

solution is stored at room temperature in a gray butyl septum sealed, sterile, pyrogen-free glass vial and has an expiration time of 8 hours.

Route of administration for this study: intravenous

Incompatibilities: no known incompatibilities

Availability: Produced at the UT Southwestern Cyclotron facility under an FDA IND

Side effects:

No adverse events have been attributed to Positron-Emission Tomography (PET) imaging/diagnostic administration of [3'-deoxy-3'-[^{18}F]fluorothymidine (FLT) at the levels injected. Therefore, no adverse events are expected as a result of the intravenous (IV) administration of ^{18}F FLT.

As with many intravenously administered agents, 3'-deoxy-3'-[^{18}F] fluorothymidine could cause an allergic reaction that could potentially pose a threat to life (anaphylaxis). This has not been observed in limited human exposure to date. Reasonable precautions will be taken, consistent with normal radiologic and clinical facility practice. The patient will be monitored until the PET procedure is completed, and trained personnel will be available per facility standards.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

We anticipate to enroll 20 patients with biopsy proven pancreatic adenocarcinoma that are not eligible for resection by the time of the diagnosis. These patients are going to be treated with chemotherapy only or chemoradiation in selected cases. These patients will undergo an optional^{18}F FDG PET/CT (as standard of care clinical baseline) and ^{18}F-FLT PET/CT before treatment (research baseline study), and after two cycles of chemotherapy (research early therapy assessment study).

For the ^{18}F-FLT PET/CT analysis, SUV max, SUV peak and proliferative tumor volume will be measured by MIMvista software and compared between the two studies. Tumor size and extension will also be evaluated on CT images from the PET/CT study.

At completion of treatment (6 months after baseline FLT PET/CT) an anatomic study (MRI or CT) will be performed as standard of care in our institution to reassess the tumor and classify it as ressectable or non-ressectable. Also at 6 months, 1 year and 2 years after initial baseline scan, or before if clinically indicated, standard of care anatomic study (MRI or CT) will also be performed and will be revaluated by RECIST criteria to determine stability versus progression of disease.

9.2 Sample size

The sample size was based on an ability to detect a relative group difference in FLT SUV (baseline versus interim) of 0.124 and standard deviation of 0.17. A sample size of 15 patients was calculated using a two-sided paired t test, power of 80 %, and the type I error rate was set to be 0.05. The expected response to therapy was assumed to be 20%[18,23,25].
Five patients were added to the sample size to compensate for dropout and no uptake on the baseline scan, leading to a total sample size of 20.

9.3 Data Analyses Plans

Primary outcome variable: The difference in SUVmax, SUVpeak and proliferative tumor volume between baseline and 2 cycles of chemotherapy will be correlated with overall survival at 1 and 2 years and with progression free survival at 6 months and at 1 year.

The primary outcome of the study is to establish which degree of change in the PET/CT quantitative parameters can predict patients overall survival and progression free survival. The SUVmax (representing the single voxel with the highest activity concentration), SUV peak (which is defined as the average SUV within a 1 cubic cm volume within the region of the tumor with the highest metabolic activity) and proliferative tumor volume of the pancreatic tumor will be measured.

Univariate and multiple cox regression model are going to be used. P-value less than 0.05 will be considered as statistical significant.

Secondary outcome variable: the difference in SUVmax, SUVpeak and proliferative tumor volume between baseline and 2 cycles of chemotherapy will be correlated with binary tumor outcome measured from MRI/CT (resectable versus non-resectable disease) at 6 month using logistic regression. A multiple logistic regression with stepwise selection algorithm will be used to select the most correlated variable(s). Areas under the ROC curve (AUC) and corresponding 95% confidence interval will be calculated for all models. Leave one out cross validation will be applied to avoid over-fit.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

10.2 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 must 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 subject 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 subject and the investigator is assured that the subject understands the implications of participating in the study, the subject 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 subject and by the person who conducted the informed consent discussion.

10.3 Registration/Randomization Procedures

There is no randomization in this study.

All subjects must be registered with the Radiology Clinical Trial Office (NE6.120) before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Clinical Trial Office Study Coordinator. To register a subject, call 214-645-2717 Monday through Friday, 9:00AM-5:00PM.

Subjects will be registered after PI has confirmed eligibility and study number will be generated in velos.

10.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for this and all SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with SCCC requirements.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

The UTSW SCCC DSMC is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.6 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, an IRB modification form must be completed within five (5) business days of making the change.

10.7 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

10.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. 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.

10.9 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring 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 retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.10 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 at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may 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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