Comparison of F-18 FDG PET CT and PET MRI with C-11 acetate PET CT and PET MRI in the diagnosis of active multiple myeloma disease: a pilot study

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Study Product: C-11 acetate

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	Comparison of F-18 FDG PET CT and PET MRI with C-11 acetate PET CT and PET MRI in the diagnosis of active multiple myeloma disease: a Pilot Study
Running Title	C-11 acetate vs. FDG with PET/CT and PET/MRI in Myeloma
Protocol Number	16-007867
Phase	*Pilot study*
Methodology	Prospective observational repeated-measure study design
Overall Study Duration	12 weeks
Subject Participation Duration	Approx. 270 minutes, over 2 days, in the nuclear medicine suite.
Single or Multi-Site	Single
Objectives	1. Our primary interest is to investigate which tracer and imaging technique combination (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) can detect more clinically significantly MM lesions compared to the standard technique (FDG PET/CT). 2. Secondary Objectives: Evaluate which tracer and imaging technique combination (FDG PET/CT, FDG PET/MRI, C11 PET/CT, C11 PET/MRI) best distinguishes the clinically significant MM lesions from other lesions detected.
Number of Subjects	10
Diagnosis and Main Inclusion Criteria	Clinically diagnosed multiple myeloma spectrum disease. Adult patients who are able to provide informed consent.
Study Product, Dose, Route, Regimen	C-11 acetate, 10 mCi, intravenous injections
Duration of Administration	Bolus injection
Reference therapy	F-18 FDG
Statistical Methodology	Objective 1. Repeated measures ANOVA. Univariate one-way repeated measures ANOVA F-test is used to calculate the sample size. Objective 2. One way repeated measure analysis of variance will be employed to detect if there is any difference among the average scores of detected MM lesion in each technique. When the sample size is 10, a single-group repeated measures analysis of variance with a 0.05 significant level will have 80% power to detect a difference in means across the 4 levels by an effect size of 0.32.

1 Introduction

This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

This project will study differing radiopharmaceutical and imaging approaches in patients with multiple myeloma spectrum disease. The use of carbon-11 (C-11) acetate as a positron emission tomography (PET) tracer to detect multiple myeloma has shown promise in a small number of recent research publications. The current standard clinical PET tracer being used, F-18 fluorodeoxyglucose (F-18 FDG), has some limitations due to the fact that up to 30% of myelomas do not show increased glucose pathway activity. In these patients, recent reports suggest that exploiting the intracellular acetate pathway rather than the glucose pathway may more reliably detect the presence of active myeloma deposits.

The study would include any consent-able adult patient over the age of 20 who is scheduled for a diagnostic FDG PET/CT scan for evaluation of multiple myeloma (MM) for the following indications: new diagnosis, high risk smoldering MM, relapse as defined by investigator.

Acetate is a key component in cellular reactions which result in the oxidative metabolism (via participation in the citric acid cycle in mitochondria), synthesis of fatty acids (in production of cell membranes), and in nuclear histone acetylation (which regulates gene expression). Cell membrane synthesis and gene expression are both important upregulated functions within cancer cells. Intravenously injected C-11 acetate is a radiopharmaceutical which acts identically to normal non-radioactive C-11 acetate in the body. The radioactivity associated with the acetate metabolic pathways can be imaged with positron emission tomographic devices, revealing and permitting visual differentiation of benign versus cancerous tissue by a radiologist.

Our study also incorporates use of a new FDA-approved hybrid PET/MRI technique. This additional modality will permit a four-way technique comparison combination which has not to date been reported.

1.2 Investigational Agent

The investigational agent for this study C-11 acetate is to be manufactured in the Mayo Clinic Arizona radiochemistry facility.

1.3 Preclinical Data

C-11 acetate has been used safely worldwide in patients with cardiovascular disease and cancer over many years. (1-7). For this study non-pharmacologic doses of C-11 acetate will be administered and should not have metabolic effects.

1.4 Clinical Data to Date

F-18 FDG is a glucose analogue that relies on tumor glucose uptake in order to reveal sites of metabolically active tumor. However, 30% of myelomas, such as the non-secretory type, have relatively low rates of glucose metabolism. (8) Recent work in cell metabolism has revealed that in the hypoxic environment of malignant tumors, glucose metabolism is shunted toward lactate production, necessitating an alternative source of acetylCoA for cell membrane fatty acid production. It is believed that in these hypoxic conditions, the acetate uptake pathway becomes a more important route to cell proliferation via cell membrane fatty acid synthesis (9, 10) and nuclear histone acetylation (important in gene transcription from nuclear DNA). (11) A small number of research studies have reported on the efficacy of C-11 acetate, with Ho et all reporting that the sensitivity / specificity of C-11 acetate PET is superior at 84.6%/100% vs. 57.7%/93.1% for F-18 FDG PET. (7)

On the technology front, combined hybrid PET/MRI devices are now FDA approved for diagnostic imaging. PET MRI may improve detection of diffuse marrow infiltration and thereby improve diagnostic utility of the PET data compared to PET CT. To our knowledge, there have been no published reports on the imaging of C-11 acetate for myeloma with PET MR.

1.5 Dose Rationale

The dose of C-11 acetate selected for use in the study patients is 10-15 mCi (370-555 MBq) based on prior published reports by Ho et al. (7). The tracer must be given intravenously.

1.6 Risks and Benefits

C-11 acetate is otherwise identical to endogenous acetate from the pharmacokinetic standpoint. Therefore the study radiopharmaceutical itself will have no nonphysiological action. The main theoretical risk involves the exposure to the radioactivity associated with the C-11 isotope incorporation. This exposure has been calculated to be lower than the standard tracer used, F-18 FDG.(see calculations). The main imaging risk involves exposure to the x-rays used to produce the CT images. However, the exposure is limited to the same low-dose technique involved in production of standard clinically performed PET/CT. Patients with contraindications to PET/MRI will be excluded (metal foreign body fragments or incompatible implanted metallic medical devices).

2 Study Objectives

Primary Objective:
Our primary interest is to investigate which tracer and imaging technique combination (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) can detect more clinically significantly MM lesions compared to the standard technique (FDG PET/CT).

Secondary Objective:
Evaluate which tracer and imaging technique combination (FDG PET/CT, FDG PET/MRI, C11 PET/CT, C11 PET/MRI) best distinguishes the clinically significant MM lesions from other lesions detected.

3 Study Design

This study will be a prospective, observational repeated-measure study to compare the standard technique of F-18 FDG PET/CT with the study techniques of F-18 FDG PET/MRI, C-11 acetate PET/CT and C-11 acetate PET/MRI in the detection of active multiple myeloma in human patients.

The doses of C-11 acetate will be administered intravenously. F-18 FDG is already an FDA-approved intravenous radiopharmaceutical. We anticipate study duration of 12 weeks, if patient recruitment proceeds as expected.

3.1 General Description

Our investigation is titled *Comparison of F-18 FDG PET CT and PET MRI with C-11 acetate PET CT and PET MRI in the diagnosis of active multiple myeloma disease: a Pilot Study.* This study will be a prospective, observational repeated-measure study to compare the standard technique of F-18 FDG PET/CT with the study techniques of F-18 FDG PET/MRI, C-11 acetate PET/CT and C-11 acetate PET/MRI in the detection of active multiple myeloma in human patients. This pilot study of 10 patients will help guide development of a subsequent future prospective study involving a larger cohort of patients. The doses of C-11 acetate will be administered intravenously. F-18 FDG is already an FDA-approved intravenous radiopharmaceutical. We anticipate study duration of 12 weeks, if patient recruitment proceeds as expected.

Our primary interest is to investigate which tracer and imaging technique combination (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) detects the greatest number of clinically significantly MM lesions compared to the standard technique (FDG PET/CT).

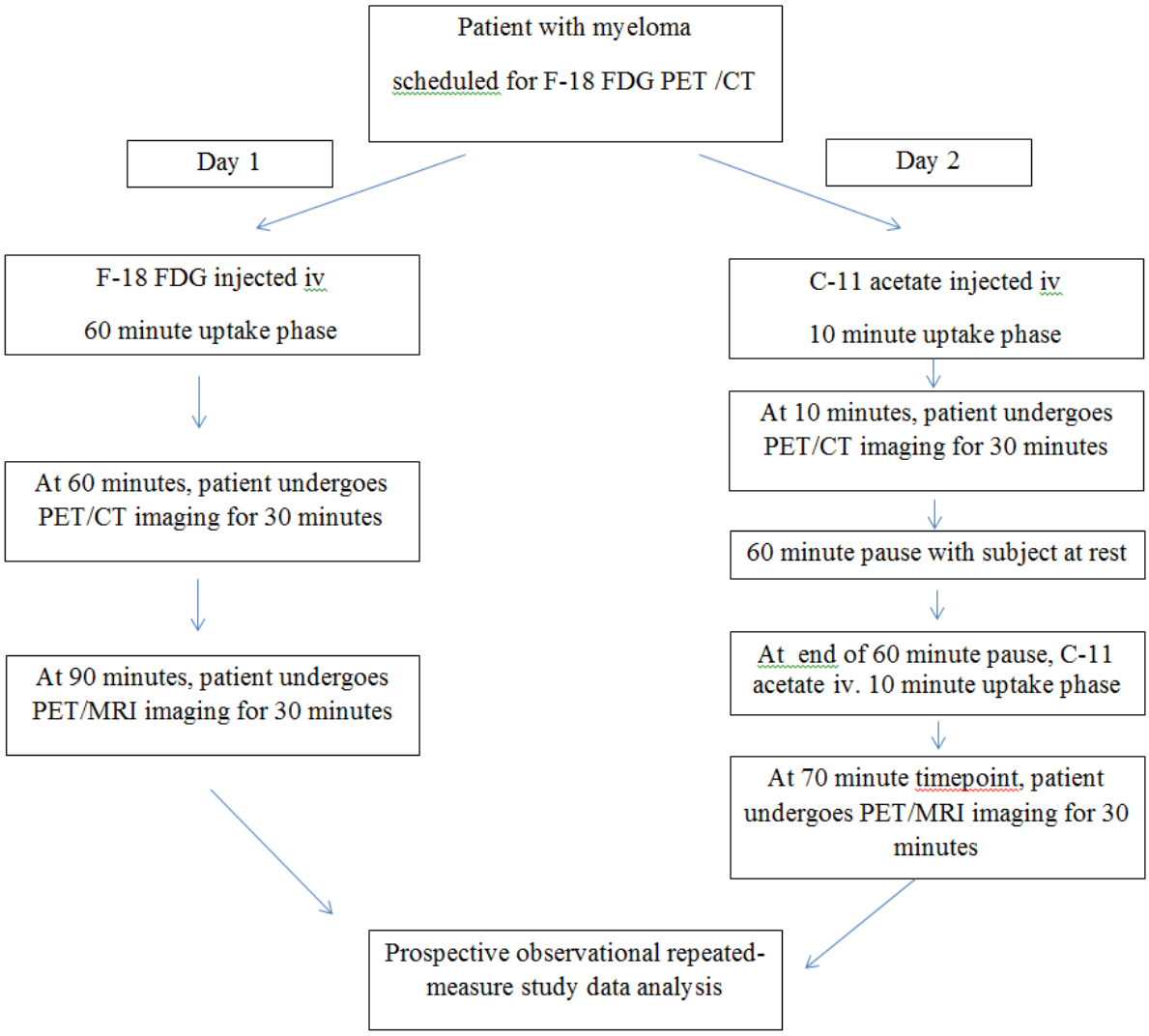
Our secondary objective is to evaluate which tracer and imaging technique combination (FDG PET/CT, FDG PET/MRI, C11 PET/CT, C11 PET/MRI) best distinguishes the clinically significant MM lesions from other lesions detected.

3.2 Number of Subjects

Ten subjects who have completed all phases of the protocol are required. In order to ensure this, it may be necessary to screen a small number of additional candidates, perhaps up to 5 total, to ensure we reach our study target of ten complete studies. For example, if an enrolled subject cannot or will not return for the second day of imaging, we will recruit and enroll a replacement subject.

3.3 Duration of Participation

There are a total of 4 visits over approximately 32 days. The first 3 visits will be at the Mayo Clinic Arizona campus. The fourth visit involves a phone call. There is an allowed 14 day window between Day 0 and Day 1. There is an allowed 14 day window between Day 1 and Day 2. There is an allowed 4 day window between Day 2 and Day 3.



3.4 Primary Study Endpoints

Our primary interest is to investigate which tracer and imaging technique combination (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) can detect more clinically significantly MM lesions compared to the standard technique (FDG PET/CT).

3.5 Secondary Study Endpoints

Evaluate which tracer and imaging technique combination (FDG PET/CT, FDG PET/MRI, C11 PET/CT, C11 PET/MRI) best distinguishes the clinically significant MM lesions from other lesions detected.

3.6 Primary Safety Endpoints

Adverse events will be monitored through the vital signs evaluated prior to and after investigational product administration.

3.7 Identification of Source Data

Source data for this study will not be directly collected in the Case Report Form (CRF), but will be captured in supportive documentation (study source documents, EMR).

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

- Patients being staged for multiple myeloma as follows: new diagnosis, high risk smoldering MM, relapsed as defined by investigator
- Patients who have undergone standard of care workup
- Patients $\geq$ 20 years old.
- 300 pounds or less
- Can provide informed consent
- Scheduled for a clinically indicated F-18 FDG PET scan
- English speaking

4.2 Exclusion Criteria

- Pregnant, breast feeding
- Concurrent active non-MM malignancy
- Contraindication to PET MRI
- Previous Type I or Type II Diabetes mellitus or a fasting blood glucose >150 mg/dl

4.3 Subject Recruitment, Enrollment and Screening

Subjects who are scheduled to undergo F-18 FDG PET/CT myeloma evaluation are identified, informed about this study and, if a potential consenting candidate, referred to our study coordinator by our heme/onc myeloma specialists from their clinical practice schedule.

4.4 Early Withdrawal of Subjects

If a subject declines to participate in the study after Day 1 of the study, no longer satisfies enrollment criteria or if the patient doesn't return for Day 2 imaging within the study timeframe, they will be withdrawn.

We plan to recruit a replacement subject in the event that a subject withdraws early to maintain the target study number of 10 subjects.

4.4.1 When and How to Withdraw Subjects

Subjects may be withdrawn from the study if consent is withdrawn, if they no longer satisfy enrollment criteria or if they are unable to continue participation due to discomfort.

Data Collection and Follow-up for Withdrawn Subjects:

The F-18 FDG PET/CT and PET/MRI data will be retained for potential future subset analysis regarding PET/CT vs. PET MRI technique. Data collected on study subjects up to the time of withdrawal will remain as part of the study in order for the study to maintain scientifically validity.

Regardless of enrollment status, subject will be contacted per Day 3 tasks for follow-up, and the case reporting documentation will be updated to include this information.

5 Study Drug

5.1 Description

Sodium Acetate C11 Injection is a positron emitting radiopharmaceutical that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. Carbon 11 is a cyclotron produced radionuclide that decays to Boron 11 by positron emission and has a physical half-life of 20.4 minutes.

[redacted]

Sodium Acetate C11 Injection is provided as a ready to use sterile, pyrogen free, clear and colorless solution.

5.2 Treatment Regimen

C11 Acetate will be injected twice for this study on the same day. Route of administration is intravenous. Dose of each injection will be 10 mCi (370 MBq). Acceptable range 5 mCi – 20 mCi.

5.3 Preparation and Administration of Study Drug

Sodium Acetate C11 Injection is prepared on site at the Mayo Clinic PET Radiochemistry Facility in Phoenix, AZ. [redacted] Due to radiation concerns, all the chemistry takes place in a fully automated chemical synthesizer located inside a 75mm lead-lined hot cell.

Following quality control testing, the drug product is packaged in a 6mL sterile shielded syringe containing approximately 20 mCi.

5.4 Packaging

The drug product is packaged in a 6mL sterile syringe containing approximately 20 mCi of radioactivity. It is placed inside a lead syringe shield and labeled with the date, batch number, radioactive assay, and drug product name. It is then placed inside a specially designed tungsten lined pneumatic tube capsule and sent to the PET imaging suite.

5.5 Receiving, Storage, Dispensing and Return

5.5.1 Storage

Sodium Acetate C 11 Injection should be stored at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) (see USP Controlled Room Temperature). The solution should be used within 60 minutes of the end of synthesis calibration time.

5.5.2 Dispensing of Study Drug

Sodium Acetate C11 is made on the day it is used. Each dose is injected in its entirety.

5.5.3 Return or Destruction of Study Drug

After injection of the Sodium Acetate C11 the syringe is assayed for residual radioactivity, to be used in calculation of the precise injected dose. The syringe is then disposed of in the radioactive container.

6 Study Procedures

6.1 Day 0

Informed consent discussion held with subject by research coordinator and consent form signed. Women of child bearing potential are required to have a serum pregnancy test. Women who are surgically sterile and/or greater than or equal to 12 months post-menopausal are not considered as child bearing potential.

Remind patient of overnight fast after 11 pm, except plain water. Review eligibility criteria to confirm all inclusion criteria are met and no exclusion criteria are met.

6.2 Day 1

1. Vital signs (sitting blood pressure, heart rate, respiratory rate, temperature) and finger-stick blood glucose are measured by the radiology nurse, who records the results on the source document.

2. Investigator MD to see patient, review vital signs and in lay language discuss study objectives, explain the imaging procedures, answer questions. MD signs and dates the source document.

3. Subject is brought to the injection room and the radiopharmaceutical is infused intravenously.

4. Subject is brought to relax room for one-hour F-18 FDG uptake period. Subject is instructed to remain at rest in the reclining chair, refrain from talking, chewing gum, or getting out of the chair for non-urgent reasons.

5. Subject is brought into the PET/CT imaging suite, placed on the scanner table, and imaging carried out.

6. Immediately following the PET/CT scan, the subject is brought to the PET/MRI suite and imaging carried out.

7. At the completion of the PET/MRI, the patient is brought back to the interview or relax room and vital signs (sitting blood pressure, heart rate, respiratory rate, temperature) are re-checked by the radiology nurse, with the research coordinator recording the results.

8. Investigator MD is called by research coordinator to perform post-procedure vital sign review, interview the patient and answer any questions.

9. Subject is discharged with instructions for overnight fast except for plain water, beginning at 11 pm.

10. Research coordinator places all study data forms in the study binder.

6.3 Day 2

1. Vital signs (sitting blood pressure, heart rate, respiratory rate, temperature) and finger-stick blood glucose are measured by the radiology nurse, and the results are recorded on the source document provided by the research coordinator.

2. Investigator MD to see patient, review vital signs and in lay language discuss study objectives, explain the imaging procedures, answer questions. MD signs and dates source document.

3. Subject is brought to the injection room and the radiopharmaceutical is infused intravenously.

4. Subject is immediately brought to the scan room, positioned on the scanning table, and at ten minutes post-injection, PET/CT performed.

5. Immediately following the PET/CT scan, the subject is brought to the relax room for a 60 minute wait at rest in the reclining chair.

6. After 60 minutes, the subject is brought to the injection room for the second C-11 acetate injection. (NOTE: If the second run of C-11 acetate fails quality control testing, steps 7-11 of the protocol would be postponed until the next day, or within one week).

7. Subject is immediately brought to the scan room, positioned on the scanning table, and at ten minutes post-injection, PET/MRI performed.

8. At the completion of the PET/MRI, the patient is brought back to the interview or relax room and vital signs (sitting blood pressure, heart rate, respiratory rate, temperature) are re-checked by the radiology nurse, who records the results on the source document provided by the research coordinator.

9. Investigator MD is called by research coordinator to perform post-procedure vital sign review, interview the patient and answer any questions. MD signs and dates the source document.

10. Subject is discharged.

11. Research coordinator places all study data forms in the study binder.

6.4 Day 3

1. Research coordinator calls patient to ask if patient has experienced fever, shortness of breath, palpitations, headache or other symptoms. If any of the above have been experienced, investigator MD is immediately notified. Subject is asked about impressions of the experience and whether they believe any additional comfort measures could have been taken.

2. Investigator MD is notified of results by the research coordinator. MD signs and dates source document.

3. All pre-data analysis study data forms and consent are confirmed intact and in the study binder. Binder is kept in a secured file cabinet in the research coordinators office.

Imaging Techniques
PET/CT: Standard clinical Mayo Clinic whole-body PET/CT acquisition protocol**.**

PET/MR: PET/MRI myeloma acquisition study protocol:

Whole Body Localizer
Station 1
Station 2
Station 3
Station 4
PET Task Whole Body
Bed 1 3:00
MRAC 1
AX LAVA-Flex 1
Bed 2 4:00
MRAC 2
AX LAVA-Flex 2
Bed 3 4:00
MRAC 3
AX LAVA-Flex 3
Bed 4 3:00
MRAC 4
AX LAVA-Flex 4
Bed 5 3:00
MRAC 5
AX LAVA-Flex 5
Bed 6 3:00
MRAC 6
AX LAVA-Flex 6
Bed 7 3:00
MRAC 7
AX LAVA-Flex 7

Comfort Modification: may remove body coils when acquisition of that area is complete, only if needed to keep the subject comfortable.

6.5 Schedule of Events

Study Activity	Day 0	Day 1 [e]	Day 2 [f]	Day 3 [g]
Informed consent	X			
History (confirm myeloma spectrum diagnosis). Record result on source document.	X			
Chart information recorded on study source document (height, weight, diabetic, pregnancy[a] and breast feeding status, bone marrow biopsy (if obtained) %, beta-2-microglobulin level (if obtained).	X			
Vital signs prior to and following imaging sessions recorded on source document (sitting blood pressure, respiratory rate, temperature, heart rate)		X	X	
Finger-stick blood glucose prior to imaging		X	X	
CBC[b], CMP[c], SPEP[d], Immunoglobulins, Serum free light chains. Within 4 weeks of study. Obtained as routine clinical tests, not research. Study coordinator will take data from EMR to enter on source/CRF.	X			
Pregnancy test (serum), if applicable [a]	X			
Adverse event evaluation. Results recorded on source document.		X	X	X
PET scans		X	X	
Follow-up call re: adverse events. Result recorded on source document.				X

[a] Women of child bearing potential are required to have a serum pregnancy test. Women who are surgically sterile and/or greater than or equal to 12 months post-menopausal are not considered as child bearing potential. Pregnant women will not be allowed to participate in this study
[b] CBC (complete blood count); red blood cells (RBCs), white blood cells (WBCs), platelets (PLTs), hemoglobin (Hgb), RBC indices, and WBC differential
[c] CMP (Comprehensive Metabolic Panel; if available, but not required to participate); Glucose, Calcium, Proteins, Albumin, Total Protein, Sodium, Potassium, CO2 (carbon dioxide, bicarbonate), Chloride, BUN (blood urea nitrogen), Creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase), AST (aspartate amino transferase), Bilirubin
[d] Serum Protein Electrophoresis
[e] Day 1 visit to occur within 14 days of Day 0 visit
[f] Day 2 visit to occur within 14 days of Day 1 visit
[g] Day 3 visit to occur within 4 days of Day 2 visit

7 Statistical Plan

7.1 Sample Size Determination

When the sample size is 10, as planned in this pilot study, a single-group repeated measures analysis of variance with a 0.05 significant level will have 80% power to detect a difference in means across the 4 levels by an effect size of 0.32. Assuming a standard deviation at each level to be 2.2 and a between level correlation to be 0.6, the average difference will be detected in this scenario is 0.78.

7.2 Statistical Methods

Descriptive Statistics

Primary Hypothesis: There is no difference in the number of clinically significant MM lesions detected by FDG PET/MRI, C11 PET/CT, C11 PET/MRI compared to the standard technique FDG PET/CT.

The patients will go through all of the 4 techniques and the number of clinically significant MM lesions detected by each technique will be collected. Our primary outcome is the number of MM lesions detected by each technique, which can vary from 0 to 13 with 5 or 6 lesions as an average for the MM patients. It is a repeated measures ANOVA design and our primary interest if to see if there is a within subject effect – if the number of MM lesions detected by each technique differ.
If the overall test is significant, post-hoc comparisons between the scores of the three new techniques (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) and the standard technique (FDG PET/CT) will be carried out with Bonferroni correction for multiple comparison.

Secondary Hypothesis 1: There is no difference in the clarity scoring of the MM lesions among the 4 techniques.

The primary interest of Objective 2 is to compare the clarity of the detected MM lesions across the 4 techniques. A score demonstrating clarity of the lesion will be assigned to each detected lesion with higher score means clearer of the lesion image. One way repeated measure analysis of variance will be employed to detect if there is any difference among the average scores of detected MM lesion in each technique. If the overall test is significant, post-hoc comparisons between the scores of the three new techniques (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) and the standard technique (FDG PET/CT) will be carried out with Bonferroni correction for multiple comparison.

Explore Objectives:
Explore which are the risk factors for having more MM lesions: CMP (Comprehensive Metabolic Panel) Glucose, Calcium, Proteins, Albumin, Total Protein, Sodium, Potassium, CO2 (carbon dioxide, bicarbonate), Chloride, BUN (blood urea nitrogen), Creatinine, ALP (alkaline phosphatase), ALT (alanine amino transferase), AST (aspartate amino transferase), Bilirubin;

SPEP (Serum Protein Electrophoresis). Immunoglobulins, Serum Free light chains; Bone marrow biopsy % and beta-2-microglobulin level (if obtained). Linear regression model with correlated data (the MM lesions detected by each technique) will be utilized to investigate the association between the potential risk factors and the number of MM lesions detected for each patient.

Handling of Missing Data
Since our sample size is 10, and they will get their imaging done in two days, we don't anticipate any missing data.

Multiplicity
We only have one primary outcome for our primary research interest. There will be no concern of multiple testing for the overall group testing. But if we see an overall effect and we will do post-hoc comparisons of the numbers of detected MM lesions between the three new techniques (FDG PET/MRI, C11 PET/CT, C11 PET/MRI) and the standard technique (FDG PET/CT). Bonferroni correction for multiple comparison will be used to address multiplicity issue.

Interim Analysis
There will not be interim analysis for our study.

7.3 Subject Population(s) for Analysis

All-completed population: Only subjects who completed ALL study related procedures and follow-up will be included

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)
Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event
An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event
Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant disability or incapacity
- birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Adverse Event Reporting Period
The study treatment follow-up period is defined as the end of the day 3 follow-up phone call for the study (1 day following the last administration of study treatment). This phone call concludes the Adverse Event Reporting Period.

Post-study Adverse Event
All unresolved adverse events should be followed by the sponsor-investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the sponsor-investigator should instruct each subject to report, to the sponsor-investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values
All laboratory values associated with this study will be a part of the patients clinical medical record, and clinically indicated. No follow up laboratory values will be obtained following imaging.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF) or in a separate adverse event worksheet. All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs during the Adverse Event Reporting Period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Sponsor-Investigator reporting: notifying the Mayo IRB

The sponsor-investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

The sponsor-investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The sponsor-investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

The relationship of an AE to the Investigational Drug is a clinical decision by the PI based on all available information at the time of the completion of the CRF and is graded as follows:

1. **Not related**: a reaction for which sufficient information exists to indicate that the etiology is unrelated to the study drug; the subject did not receive the study medication or the temporal sequence of the AE onset relative to administration of the study medication is not reasonable or the event is c1early related to other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.

2. **Unlikely**: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

3. **Possible**: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but which could also be explained by concurrent disease or other drugs or chemicals; information on drug withdrawals may be lacking are unclear.

4. **Probable**: a clinical event including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (de-challenge): re-challenge information is not required to fulfi1 this definition.

5. **Definite**: a reaction that follows a reasonable temporal sequence from administration of the drug, or in which the drug level has been established in body fluids or tissues, that follows a known or expected response pattern to the suspected drug, and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure (re-challenge).

The maximum intensity of an AE during a day should be graded according to the definitions below and recorded in details as indicated on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates.

1. Mild: AEs are usually transient, requiring no special treatment, and do not interfere with patient's daily activities.

2. Moderate: AEs typically introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

3. Severe: AEs interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

8.4 Stopping Rules

Stopping rules not applicable as standard radiology safety procedures will be followed.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

Data Management

CRFs will be organized in a binder, maintained in a locked cabinet in the research coordinator's office.

A dedicated Excel spreadsheet, with track-changes enabled, will be maintained in a secure folder discussed above. This spreadsheet will serve as the data aggregation instrument.

Data Processing

The data will be analyzed via the statistical methods outlined in this document.

Data Security and Confidentiality

A study-specific Excel spreadsheet is employed to consolidate and analyze data from the written CRFs and printed data from the EMR. It will be a password protected file within a secured folder with permissions limited to study staff on the RADPUBLIC server. This constitutes several layers of permissions one must pass in order to access the Excel sheet. Patient-specific information will only be available on the written CRF. Only the patient number will be entered on the spreadsheet.

Data Quality Assurance
Any data copied over from the written CRFs or the EMR will be double checked by the study staff member who does the entering in an ongoing basis during the study. The CRFs and EMR lab printouts will be kept in the study binder. At the end of the study, the PI, Co-PI or a Co-investigator will again double check all data entered into the spreadsheet from the CRFs and printout EMR sheets for each subject to detect any transcription errors.

9.4 Records Retention

The sponsor-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The sponsor-investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The Principal Investigator will review study process, progress, and data security in conjunction with the research coordinator. Review of study progress every 2 weeks on a regular basis and documentation of this review in study review log, even when there are not irregularities or remedial measures which need to be taken.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study will be funded in part by a grant from the Mayo Clinic Clinical Research Subcommittee Arizona Opportunity Fund; these funds must be used within the 2016 calendar year only. These funds will not carry over into 2017 or beyond. Any additional funds that may be needed will be supplied by the Mayo Clinic Arizona Radiology Department.

13 Publication Plan

We intend to submit the results of this pilot study for publication to nuclear medicine, molecular imaging, or oncology journals as is deemed justified by the results of the data analysis. P.I. Dr. Roarke, in conjunction with Co-I. Dr. Fonseca, will determine the best publication plan to pursue. Permission and agreement will be sought from each co-author attached to this project.

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