Multicenter, Phase II Assessment of Tumor Hypoxia in Glioblastoma Using $^{18}$F-Fluoromisonidazole (FMISO) with PET and MRI
Dear PET Imaging Staff,
The PET Image Management Plan contains instructions for all aspects of carrying out the PET imaging component of the ACRIN 6684 trial: A Multicenter, Phase II Assessment of Tumor Hypoxia in Glioblastoma Using $^{18}$F-Fluoromisonidazole (FMISO) With PET and MRI.

For the study objectives to be successfully met, it is critical that you acquire the PET images according to the imaging protocol detailed in this plan. Because the PET imaging protocol required for this study may be new for your site, and perhaps this may be your first time supporting an ACRIN clinical trial, I will be conducting an onsite visit to review the imaging parameters to ensure you are ready to confidently scan your first study participant.

During the site visit, I will also review the mandatory forms to be completed at the time of each PET scan acquisition as well as the instructions included in the plan for submitting images to the core laboratory at ACRIN headquarters in Philadelphia, PA.

Part of ACRIN standard procedures is a quality control (QC) review of the images sent to the core laboratory. Should a core laboratory technologist performing the QC review identify any protocol violations or technical issues, he or she will provide expedient feedback so that you can make the necessary adjustments.

Thank you in advance for your diligent efforts in adhering to the procedures described in the image management plan and for helping us ensure the compliance and integrity of the image data collected for the ACRIN 6684 study. I look forward to collaborating with you!

Sincerely,

Adam Opanowski, CNMT,RT (N)
215-940-8890
aopanowski@acr-arrs.org
ACRIN 6684 Study Schema and Objectives

**Sample Size**
A total of 50 participants will be enrolled. The first 15 participants will have test/retest FMISO PET scans at baseline performed between 1 and 7 days apart (both scans completed prior to initiation of chemoradiation). The recruitment time frame is approximately 1 year. Each of the four to ten participating institutions will enroll no more than 15 participants to this trial.

**Primary Objective**
To determine the association of baseline FMISO PET uptake (hypoxic volume [HV], highest tumor:blood ratio [T/B$_{max}$]) and MRI parameters ($K^{trans}$, CBV) with overall survival (OS) in participants with newly diagnosed GBM.

**Secondary Aims**
Aim 1: To determine the association of baseline FMISO PET uptake (HV, T/B$_{max}$) and MRI parameters ($K^{trans}$, CBV) with time to progression (TTP) and 6-month progression-free survival (PFS-6) in participants with newly diagnosed GBM.

Aim 2: To determine whether change on FMISO PET uptake and MRI parameters from baseline to week 4 is associated with OS, TTP, and PFS-6 in participants with newly diagnosed GBM.

Aim 3: To determine whether change on FMISO PET uptake and MRI parameters from baseline to week 10 is associated with OS, TTP, and PFS-6 in participants with newly diagnosed GBM.

Aim 4: To assess the reproducibility of the baseline FMISO PET uptake parameters by implementing baseline “test” and “retest” PET scans (performed within 1 to 7 days of each other).

Aim 5: To assess the correlation between highest tissue:cerebellum ratio [$T/C_{max}$] and T/B$_{max}$ at baseline, week 4, and week 10.

Aim 6: To assess the correlation between other MRI parameters (T1Gd, VCI, CBV-S, ADC, NAA-Cho, T2) and OS, TTP, and PFS-6.
PET Scan Time Points/Visits

All patients will undergo baseline $^{18}$F-FMISO PET and MRI studies 2 to 4 weeks after initial debulking surgery and prior to radiotherapy (XRT) (T0). Additionally, imaging will be performed after 3 weeks of radiotherapy (T1) and 4 weeks after the radiation is complete, before the second cycle of temozolomide (TMZ) (T2).

**Note:** Please work with the RA and persons responsible for scheduling the PET and MRI scans to accommodate study participants’ preference for either undergoing the MRI and PET scans on the same day OR scheduling the scans on separate days, but not longer than 2 days apart per the protocol.

<table>
<thead>
<tr>
<th>Table 1. TREATMENT AND IMAGING</th>
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<tbody>
<tr>
<td><strong>Visit 2</strong></td>
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<tr>
<td>Baseline</td>
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<tr>
<td>TMZ (mg/m²/day)</td>
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<tr>
<td>Radiation Therapy</td>
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<tr>
<td>FMISOPET Scan</td>
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<tr>
<td>Brain MRI Scan With Contrast‡</td>
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</table>

† The first 15 participants will have two baseline $^{18}$F-fluoromisonisazole (FMISO) PET scans performed 1 to 7 days apart for test/retest analysis (see protocol section 9.2.1 for details of visit 2A); both scans must be completed prior to initiation of chemoradiation.

‡ All MRIs (with or without contrast) and CTs performed as standard of care during participant follow-up should be submitted to ACRIN (see protocol section 10.4, “Image Submission Criteria,” for details).
PET Scanner Qualification Procedures

ACRIN qualification of a site’s PET or PET/CT scanner is required prior to enrollment of study participants. If the scanner to be used for this trial is already qualified by ACRIN, a site does not need to complete the qualification application, as long as the 2-year PET qualification period has not expired. If the qualification has expired, a site will need to complete a new application. In addition, all sites must complete the “well counter qualification,” even if the PET scanner does not need to be qualified or requalified.

The application instructions and the application form are available on the ACRIN 6684 protocol-specific Web page (click on the “Imaging Materials” section) at www.acrin.org/6684_protocol.aspx.

Note: If your PET scanner must be qualified, or requalified, please submit PET brain images versus the body images specified in the application.

Daily Quality Control Requirements

A daily (QC check must be performed at the beginning of the day a study participant is to be scanned. The QC check must include the PET scanner, dose calibrator, and well counter, in accordance with the manufacturer recommendations.

Note: If any of the QC results are outside of the manufacturer’s guidelines, the study must be rescheduled and the problem resolved prior to scanning a study participant.

For the ACRIN-qualified PET scanner:

- Keep calibrated in accordance with the manufacturer’s recommendations.
- Routinely assess the scanner for quantitative integrity and stability by scanning a standard quality control phantom with the same acquisition and reconstruction protocols as those used for study participants.
- Perform standard uptake value (SUV) verification measurements to include the dose calibrator used to measure the doses of study participants, to ensure that the dose calibrator and PET scanner are properly cross-calibrated (ie, the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images).
- Perform a QC (empty port transmission) scan at the beginning of the day a study scan is to be completed. The QC sinogram should be visually inspected for abnormalities.

For the dose calibrator:
- Perform QC of the dose calibrator throughout the course of the study. This typically will include daily constancy, quarterly linearity, and annual accuracy tests, all of which should be documented.

Well Counter Calibration Procedures

**NOTE:** As a pre-qualification measure, sites will need to demonstrate appropriate well counter cross calibration.

1. The time of all measurements should be documented in reference to a single clock. If possible, the clocks on the PET scanner, well counter, and dose calibrator (if it has a clock) should be synchronized to this reference clock.
2. Fill a uniform cylindrical phantom (18-22 cm diameter) with water and eliminate as many air bubbles as possible.
3. Fill a syringe with a sufficient activity of $^{18}$F to achieve a concentration in the phantom of approximately 0.2 µCi/mL. Make sure the syringe is properly placed inside the dose calibrator. Assay the syringe activity in the dose calibrator and record the assay result in mCi and the assay time.
4. Withdraw approximately 60 mL of water from the phantom using a large syringe and an 18-gauge needle.
5. Add the $^{18}$F into the phantom and thoroughly rinse the syringe contents into the phantom. Assay the residual activity in the syringe in the dose calibrator and record the assay result and assay time, seal the phantom and repeatedly invert to mix the solutions. Enter the measured full syringe activity (mCi), measured full syringe activity assay time, residual syringe activity (mCi), residual syringe activity assay time, and volume of the completely filled phantom (mL) in the EXCEL spreadsheet. [Note: The phantom volume should be obtained from the manufacturer of the phantom.]
6. Add water to the phantom to fill it completely. Re-seal and thoroughly mix the contents of the phantom, to make sure that the $^{18}$F is uniformly distributed.
7. Using a calibrated balance (with at least 1 mg precision), weigh each of three (labeled 1,2,3) gamma counting tubes with their respective caps, and enter the weight of each gamma counting tube (including cap) separately in the EXCEL spreadsheet.
8. Withdraw three 1.0 mL samples from the phantom with a syringe or pipette and place into the weighed gamma counting tubes from Step 7. Replace the cap on each gamma counting tube.

9. Re-seal the phantom and position in the center of the PET scanner gantry using the phantom holder supplied with the scanner.

10. Perform a 20-minute static scan of the phantom using identical acquisition and reconstruction parameters as are used for FMISO patient acquisitions.

11. Using the same calibrated balance as in step 7, weigh each of the gamma counting tubes containing the samples and enter the results in the EXCEL spreadsheet.

12. With a pipette or syringe, place 1.0 mL of tap water into a gamma counting tube labeled ‘BKG’ for measuring background radiation.

13. Count each of the samples and the BKG tube in the well counter for 60 seconds using a counting window set for 511 keV photons, or close equivalent. Enter the counting results and start times of the counting of each sample into the EXCEL spreadsheet.

14. The formulas in the spreadsheet will combine the weight of the samples and the number of counts per minute and display the well counter rate concentration, \( R_{(wc)} \) (cpm/mL), decay corrected back to the start time of the PET scan. The cpm/mL is calculated by dividing by the net volume of the sample in the gamma counting tube, assuming a density of 1 g/mL.

15. Upon completion of the image reconstruction, measure the mean SUV (based on weight) by drawing a large circular ROI, on one plane and then copying that ROI, to all planes (EXCEPT THE FIRST AND THE LAST PLANE). Average the mean SUVs for all the ROI’s throughout the phantom as measured by the PET scanner.

16. Using the EXCEL spreadsheet provided, enter the data from the procedure above to compute the cross-calibration factor.

17. The calibration factor (CF) between the well counter and the PET scanner is calculated as follows:

\[
CF = \frac{PET}{R_{(wc)}}
\]

**Note:** The units of CF are SUV/(cpm/mL), which is used by multiplying the sample cpm/mL to convert the units to sample SUV.
Well Counter Cross-Calibration Spreadsheet

Note: Print out spreadsheet prior to scanning.

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<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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Blood Sampling Procedures

**Note:** Prior to study site activation, demonstration of appropriate cross-calibration of the PET scanner is required. Use of a dose calibrator, rather than a NaI-detector well counter, for counting of blood samples is strictly prohibited, because the dose calibrator is not sensitive enough for the required activity measurements. Prior to performing the study, print out the Blood Sampling (BS) Form for completion during the procedure. Data recorded on the form will need to be entered into ACRIN’s Web-based form. Step-by-step instructions regarding blood sampling procedures follow:

1. The time of each blood draw and of all measurements should be documented in reference to a single clock. If possible, the clocks on the PET scanner, well counter, and dose calibrator (if it has a clock) should be synchronized to this reference clock.

2. The well counter being used should have a CF determination within 1 week prior to the study (see Appendix III). The value and the date of calibration must be entered on the FMISO PET BS Form.

3. Three venous blood samples should be obtained at intervals of 5 minutes (± 2 minutes), at 5, 10, and 15 minutes after the start of emission scanning. The exact time of the blood draws must be recorded.

4. The blood samples must be drawn from the IV placed in the arm opposite the one used for the FMISO injection.

5. To avoid dilution, 3–5 mL of blood must be drawn for “waste” prior to withdrawing each of the blood samples.
6. Withdraw 3–5 mL of blood for each sample.

7. Use a calibrated balance (with at least 1 mg precision) to weigh each of 3 gamma counting tubes with their respective caps. Enter the weight of each gamma counting tube (including cap) on the BS Form.

8. After weighing the empty gamma counting tube with cap, expel from the sample syringe approximately 1.0 mL of blood and transfer the sample into the gamma counting tube with another syringe or pipette and cap the tube.

9. Using the same calibrated balance as in step 7, weigh each of the sample gamma counting tubes and enter the results on the BS Form.

10. Background counts must be measured in the well counter prior to counting each of the blood samples. The background count must be performed with nothing in the well counter for an interval of 2 minutes. Results must be recorded on the BS Form.

11. Following the background measurement, count the gamma counting tube containing the blood sample for 2 minutes. Results must be recorded on the BS Form.

12. It is preferable to count the blood samples after all three have been collected.

13. Provide the form to the research associate for entering data in the Web-based form.

ACRIN 6684 Blood Sampling Form

Note: Print out BS form prior to scanning.
Study Participant Preparation and Positioning

Please be aware of the following for the study participants:

- No deliberate fasting is required prior to injection.
- Encourage participants to be well hydrated prior to the scan.
- Blood glucose measurement is not required.
- Participant’s height and weight must be measured using calibrated and medically approved devices (not verbally relayed by the participant).

**Note:** Serial scans of the same participant must be done on the same scanner for this study.
FMISO PET Imaging Protocol

Following are the steps for conducting the PET scan for the ACRIN 6684 study. To aid data entry, print out the TA, BS, and ITW forms along with the Well Counter Cross-Calibration spreadsheet prior to scanning. Enter data on paper forms for later entry in the respective Web form or spreadsheet.

**Note:** *Exact time collection is key to the success of this protocol.* A global time piece (eg, a portable stop watch) should be used consistently as a standardized measuring tool throughout the trial for all time collection. The time piece will need to accurately record minutes, at the least, and preferably seconds as well. It will be used to collect time at dose counting, injection time, imaging start time, blood sampling time, and blood counting time.

1. **Injection of FMISO**
   - Two IV catheter access lines (18 or 20 gauge is preferred) are placed, one in each arm—one for the FMISO injection and the other for blood sampling during the scan.
   - The dose of FMISO is 3.7 MBq/kg (0.1 mCi/kg) (maximum 260 MBq, 7 mCi) in < 15 mL. For the FMISO injection, minimize the length of the IV tubing between the injection site and the vein to avoid FMISO being left in the tube.
   - A saline flush should follow the FMISO injection.
   - The exact time of calibration of the dose should be recorded using the study-designated standardized global time piece; the exact time of injection should be noted and recorded to permit correction of the administered dose for radioactive decay. In addition, any of the dose remaining in the tubing or syringe, or that was spilled during injection, should be recorded. The injection should be performed through an IV catheter and 3-way stopcock.
   - Adverse events (AEs) should be solicited in an open-ended fashion (ie, “How are you feeling?”) at this time.

2. **FMISO PET Imaging**
   - Single field-of-view emission imaging must begin 110 ± 10 minutes after FMISO injection. Imaging start time should be recorded using the study-designated standard global time piece.
   - The participant should empty his/her bladder immediately before the acquisition of images.
   - Participants should be imaged in the supine position with head immobilization. Head immobilization procedures for PET imaging are site-specific.
   - An attenuation scan should be performed prior to emission scanning, or just after emission scanning if necessary. The transmission scan should be a low-dose CT scan for the PET/CT or a transmission scan for PET-only devices. Characteristics of the transmission scan (eg, type, length) should exactly match those used in the calibration and qualification procedure.
- A 20-minute emission scan is then performed.

- During emission tomography, 3 venous blood samples are obtained at intervals of 5 minutes (± 2 minutes). Blood must be drawn from the IV that was not used for the FMISO injection. The exact time of the blood draws should be recorded using the study-designated standard global time piece.

- Whole blood samples of 1 mL each are counted (within 60 minutes of collection) in a multichannel gamma well counter that is calibrated each week in units of cpm/uCi (refer to Well Counter Calibration Instructions and Blood Sampling Procedures).

- The exact time that each blood sample is counted should be recorded using the study-designated standard global time piece.

- Blood activity is averaged and then expressed as uCi/mL, decay-corrected to the time of injection.

### Timing Sequence for FMISO Injection and PET Imaging

#### Note:
Global time will need to be recorded for dose counting, injection time, imaging start time, blood sampling time, and blood counting time throughout the trial.

### 3. FMISO PET Imaging Reconstruction Protocol

- The PET data are corrected for dead time, scatter, random, and attenuation using standard algorithms provided by the scanner manufacturer.

- Image reconstruction is performed as specified in the ACRIN certification of the PET scanner.

### PET Image Submission Requirements and Options

Sites have two options for submitting MR images to ACRIN’s image archive.
- Using ACRIN’s image transfer application (TRIAD). This is the preferred method.
- Express mailing images on a CD-ROM

**Note:** All PET images for this protocol must be provided in DICOM format.

**TRIAD software for SFTP submission**

The preferred image transfer method is via TRIAD, a software application that ACRIN provides for installation on a site’s PC. TRIAD collects image sets from a scanner’s computer or from the picture archiving communications system (PACS). The TRIAD software anonymizes, encrypts, and nondestructively compresses the images as they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software. For more information, contact: **TRIADsupport@phila.acr.org**.

Upon electronically submitting the PET images, sites should fax the Image Transmittal Worksheet (see “Image Transmittal Worksheet Instructions”) to the ACRIN core laboratory at 215-923-1737 or e-mail it to **aeg-7335@acr-arrs.org**.

**Media delivery instructions**

For exams submitted via a CD-ROM, please affix a label to the CD jacket that includes: study name, site name, site number, subject number, date of scan(s), image time point, and type of imaging. Do not apply adhesive labels directly to the CD.

Complete the Image Transmittal Worksheet (see “Image Transmittal Worksheet Instructions”) and include it with the media shipment.

Mail the images and worksheet to:

**American College of Radiology Imaging Network**  
**PET Core Laboratory**  
**Attn: ACRIN 6684**  
**1818 Market Street, 16th floor**  
**Philadelphia, PA 19103**

**Image Transmittal Worksheet Instructions**

The Image Transmittal Worksheet (ITW) below can also be found on the protocol-specific page of the ACRIN Web site: www.acrin.org/6684_protocol.aspx (click on “Imaging Materials”).

PET images are required to be submitted to ACRIN after each time point (or visit) that must be recorded on the ITW. The ITW must include the site number/subject number, as well as the name of the technologist performing the scan. Other information required on this form includes the time point, date of study, participant date of birth (for quality control purposes), and mode of image submission (submission via TRIAD is preferred).

Sites must also provide the e-mail address of the person who should receive feedback regarding image quality. An ACRIN core laboratory imaging specialist reviews the ITW in order to confirm the number of
PET Image Transmission Worksheet

Note:
- Images will not be credited as received at ACRIN without the submission of a fully completed ITW.
- A fully completed ITW is required for each case submitted.
- Careful completion of this form will avoid having to respond to queries.

**PET Images:**
Imaging studies must be submitted to the core laboratory after each time point/visit along with a fully completed, signed ITW. **Keep a copy for your records.**
- For images submitted via TRIAD, complete this worksheet and fax it to: 215-923-1737, or e-mail it to: ACRIN6684PET@acr-arrs.org.
- For images submitted via a mailed CD-ROM, complete this worksheet and include it with the media shipment. Please affix a label to the jacket of the media to include: study name, site name and number, case number, date of exam(s), time point, and type of imaging. **Do not affix adhesive labels directly to the CD.**

**Well Counter Cross-Calibration Forms:**
Submit a completed well counter cross-calibration spreadsheet for each case via e-mail to ACRIN6684PET@acr-arrs.org.

**Questions?** Please contact Adam Opanowski, CNMT, RT (N) at 215-940-8890 or aopanowski@acr-arrs.org.

### Section I: Image Data Demographics

<table>
<thead>
<tr>
<th>Site Number:</th>
<th>Case Number:</th>
<th>Type of Scanner:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PET/CT ☐, PET/MRI ☐, PET only ☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient DOB:</th>
<th>Study Date</th>
<th>Participant Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-11-19</td>
<td>11-11-20</td>
<td>First</td>
</tr>
</tbody>
</table>

| Time Point: | Baseline ☐, Visit 3 ☐, Visit 4 ☐, Follow-up/Final ☐ |

**Images from an ACRIN-Approved Scanner?** Yes ☐, No ☐
**Record Scanner Model and Station:**

### Section II: Data Being Submitted:

- [ ] FMISO PET Scan
- [ ] PET Technical Assessment (TA) Form
- [ ] Cross-Calibration Spreadsheet
- [ ] Blood Sampling Form

**Institution Comments:**

**Form Completed By:**

| Phone: | E-mail: | Date: |

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**Quality Control Procedures**

ACRIN imaging specialists review all ITWs and images submitted to ensure images comply with the protocol parameters. Should the specialist discover that images or image-related data are missing, inaccurate, or inconsistent with the imaging protocol, sites are notified through the following process:

1. An **imaging query** describing the problem is e-mailed to the study coordinator. Such a query is also referred to as a Z5 form (see example below).

2. The site should resolve the problem as quickly as possible and must maintain a hard copy of the completed and signed query at the site.
3. A site receives up to three reminders to resolve a query. After that time, an outstanding query is reported to the trial leadership for assistance with resolution.

Request for Additional Imaging Information

<table>
<thead>
<tr>
<th>Image Type</th>
<th>Study Date</th>
<th>Explanation</th>
<th>Site Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing Images/Views - Study incomplete (<strong>Site Comments</strong>)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Date of Birth (DOB) on Images does not match DOB in Clinical DB. Please Confirm correct DOB. (<strong>Site Comments</strong>)</td>
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<tr>
<td>Anatomy Not Covered (ANC) (<strong>Site Comments</strong>)</td>
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<tr>
<td>Poor Quality Images (<strong>Site Comments</strong>)</td>
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<tr>
<td>Incorrect Case # assigned to images (<strong>Site Comments</strong>)</td>
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<tr>
<td>Incorrect technical factors utilized (<strong>Site Comments</strong>)</td>
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<td></td>
</tr>
<tr>
<td>OTHER (<strong>Site Comments</strong>)</td>
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<td></td>
</tr>
</tbody>
</table>

ACRIN Comments:  
SITE Comments:

Institution Representative: ______________________  Phone No. _______  Email: ______________________

Signature: ______________________  Date: ______________________