ACRIN 6684

PATHOLOGY TISSUE PROCESS MANUAL
TABLE OF CONTENTS

1. INTRODUCTION ........................................................................................................................................2
   1.1 Study Objectives ...............................................................................................................................2
   1.2 Scientific Background ......................................................................................................................2

2. SAMPLE SELECTION .................................................................................................................................3
   2.1 Selection Criteria .............................................................................................................................3
   2.2 Contacting Pathology Departments/Laboratories ........................................................................3

3. REQUESTING SPECIMENS FROM LENDING PATHOLOGY LABS .................................................................3
   3.1 Request Packets ................................................................................................................................3
       3.1.1 Pathology Request Cover Letter ...............................................................................................4
       3.1.2 Pathology Specimen Collection—Request Form .......................................................................4
       3.1.3 Authorization to Release Surgical Material .............................................................................4
       3.1.4 HIPAA Authorization ..............................................................................................................4
       3.1.5 Pathology Report .....................................................................................................................4
       3.1.6 Shipping Materials for Lending Pathology Laboratories .........................................................4
   3.2 Pathology Laboratory Non-Response Follow-Up for Specimen Request .......................................5

4. COLLECTING SPECIMENS AT STUDY CENTERS ....................................................................................5
   4.1 Receiving Specimens from Lending Pathology Laboratories .........................................................5
   4.2 Labeling and Storing Specimens from Lending Pathology Labs ....................................................5

5. MAINTAINING AND SHIPPING SPECIMENS TO PATHOLOGY CORE FACILITY ....................................7
   5.1 Shipping Materials and Process .....................................................................................................7
   5.2 Labeling Shipping Containers .......................................................................................................7
   5.3 Summary Shipping Task List ..........................................................................................................8

6. RETURNING LOANED SPECIMENS ........................................................................................................8
   Appendix I Authorization Cover Letter Template .................................................................................9
   Appendix II Authorization to Release Surgical Material Template ....................................................10
   Appendix III Participant Non-Response Log: (Request for Authorization) ........................................11
   Appendix IV-A Pathology Request Cover Letter Template (Blocks Request) ......................................12
   Appendix IV-B Pathology Request Cover Letter Template (Slides Request) .......................................13
   Appendix V-A Pathology Specimen Collection (Block Request Form) ................................................14
   Appendix V-B Pathology Specimen Collection (Slide Request Form) .................................................15
   Appendix VI Pathology Laboratory Non-Response Log: (Request for Specimen(s)) ..........................16
   Appendix VII Discrepancy Notification Form ....................................................................................17
1. **INTRODUCTION**

1.1 **Study Objectives**

Primary Aim

To determine the association of baseline FMISO PET uptake (hypoxic volume [HV], highest tumor:blood ratio [T/Bmax]) and MRI parameters (Ktrans, 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/Bmax) and MRI parameters (Ktrans, 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/Cmax] and T/Bmax 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.

Aim 7: To investigate the possible relationships between hypoxic biomarkers and FMISO uptake with progression-free survival and overall survival, tumor tissue obtained for diagnosis of glioblastoma will be analyzed for expression of hypoxic and vascular markers.

1.2 **Scientific Background**

Glioblastoma (GBM) is the most common and, unfortunately, most aggressive type of primary malignant brain tumor. Despite treatment with surgery, radiation, and temozolomide (TMZ) chemotherapy, median overall survival (OS) is less than 15 months. One of the pathologic hallmarks of GBM is necrosis, thought to be the result of tumor hypoxia secondary to an inefficient blood supply. Hypoxia is a potent stimulator of angiogenesis, a requisite for tumor growth. In addition, hypoxia limits the efficacy of radiation and chemotherapy. By better understanding the extent of tumor hypoxia and changes in regional tumor hypoxia with treatment, more effective and patient-specific therapies could be devised to halt GBM growth. 18F-Fluoromisonidazole (FMISO) PET is a non-invasive method that can estimate tissue hypoxia. New advanced MRI methods, such as dynamic contrast enhanced (DCE) MRI, oxygen breathing during BOLD imaging, vessel caliber mapping, or other approaches may contribute to characterization of tumor physiology and/or prognostic information for patients with GBM. Combining such vascular-imaging methods with hypoxia data from FMISO uptake is very attractive. We propose using these PET and MRI techniques hand in hand to monitor the standard initial treatment of patients with GBM and to perform pilot work to determine if FMISO PET may be a useful predictive or prognostic marker in patients with GBM undergoing standard of care treatment with radiation and TMZ. Although the primary aim is to establish hypoxia imaging as a tool to select more aggressive and/or hypoxia-targeted therapy in particular subsets of patients, understanding how chemoradiation affects hypoxia and tumor vascularity is an important complimentary aspect of the study. In this study, participants with residual GBM after surgery will undergo FMISO PET and MRI scans prior to start of chemoradiation (baseline), 3 weeks after the start of chemoradiation (week 4), and then 4 weeks following completion of chemoradiation (week 10). The first 15 participants will have two FMISO PET scans within 1 to 7 days of each other and prior to Visit 2 to test reproducibility of FMISO PET. Participants will then resume standard of care imaging for GBM per treating physician
discretion. Participants will be followed for up to 3 years from study entry unless death occurs first.

2. **Sample Selection**

2.1 **Selection Criteria**

The selection criteria for pathology tissue collection will include all participants in 6684:

- Who have been newly diagnosed with GBM (World Health Organization [WHO] grade IV)
- Whose had an operative procedure and tumor have been resected
- Signed a Study Consent Form (See Section 2.4 - “Informed Consent”)

For each participant, the site should collect the following documentation:

- Original pathology report. Procure ALL pathology reports, as there may be multiple reports if there were separate surgeries
- Operative report(s) corresponding to the pathology report.

2.2 **Contacting Pathology Departments/Laboratories**

The Pathology Report documenting the diagnosis of GBM will identify the source pathology laboratory. The site should contact the pathology laboratory to establish a relationship and to procure contact information, including: the name, phone number, e-mail address, fax number, and shipping address of a contact person at the laboratory for specimen collection.

The lending pathology laboratories may require specific documentation before the release of surgical tissues, including:

- Signed informed consent
- Signed Authorization to Release Surgical Material
- HIPAA authorization (or equivalent form prior to HIPAA enactment)
- Their own institutional forms
- Any combination of the above
- No documentation

It is strongly recommended that sites contact the laboratories to determine exactly what they will require prior to making specific requests for tissues.

The site should also determine the pathology laboratory’s policies on specimen loans (in particular, policies on release of blocks versus unstained sections), costs for requesting specimens, whether the lab is willing to grant permanent retention of the specimens or, if not, the maximum loan period permitted. The site should inform the lab that a minimum loan period of three (3) months required to ensure adequate time for shipping and processing. Payment for requests, if required by the pathology laboratory, should be managed by the site in

3. **Requesting Specimens from Lending Pathology Labs**

**NOTE:** As cases will be processed for biomarker analyses in batches, requests for tissue should **NOT** be initiated until instructed to do so by Rosa Medina from ACRIN headquarters.

3.1 **Request Packets**

Once participant consent and authorization is established, the ACRIN 6684 site coordinator should assemble a request packet for each pathology laboratory. Specimens from multiple participants may be requested from a single pathology laboratory in one packet. Each request packet will include the following items (which are included as appendices to this manual and are explained in detail in the following sections):

1. **Pathology Request Cover Letter (Appendix IV)** signed by the ACRIN 6684 Site Principal Investigator (PI) or designee.
2. **Pathology Specimen Collection—Request Form(s) (Appendix V-A or V-B)** that specifies the requested histologies. This will be used by the pathology laboratory to document release of the specimens or the reasons for which specimens were not provided.

3. Copies of the participant(s) **Authorization to Release Surgical Material (Appendix II)** or comparable authorization according to the pathology labs policies.

4. **Pathology report** for all participants included in each pathology laboratory request. These items are included as appendices to this manual and are explained in detail in the following sections.

### 3.1.1 Pathology Request Cover Letter

The Pathology Request Cover Letter (Appendix IV-A or IV-B) briefly explains the purpose of the request, how loaned tissue blocks will be processed and returned or the number of slides needed in lieu of tissue blocks. Both appendixes will also explain how to ship the specimens to the ACRIN 6684 site.

### 3.1.2 Pathology Specimen Collection—Request Form

The Pathology Specimen Collection—Request Form (Appendix V-A and V-B) will be used by lending pathology departments to indicate the release of specific specimen types and their unique paraffin block/slide identification, or to indicate problems associated with fulfilling the request. The ACRIN 6684 Site coordinator will always use Appendix V-A first to request tissue blocks because it is the preferred specimen type. If the lending pathology laboratory returns the pathology request form (Appendix V-A) indicating that they do not loan tissue blocks then the site coordinator will follow up requesting slides using Appendix V-B. The ACRIN 6684 site coordinator is responsible for filling out the pertinent participant information at the top of the form and the Date of procedure for each block/slides that is being requested before sending the form to the lending pathology laboratory. The form should be returned by the lending pathology laboratory to ACRIN 6684 sites along with specimen blocks/slides, or returned alone to indicate barriers or reasons for refusal to provide tissues.

Note that a Pathology Specimen Collection—Request Form should be provided for each individual participant. Multiple forms may be included in a request packet if specimens from multiple participants are requested at one time. If a pathology laboratory does not return a filled out Pathology Specimen Collection Form (A or B), the site RA is responsible for filling out a "Note to File". Please document if you received specimen(s) or not and the reason for not getting a returned form. A copy of the “Note to File” should be retained in the participants chart.

### 3.1.3 Authorization to Release Surgical Material

The signed Authorization to Release Surgical Material (Appendix II) should be attached to the Pathology Request Cover Letter, if specifically required by the pathology laboratory.

### 3.1.4 HIPAA Authorization

A copy of the site’s HIPAA Authorization should be attached to the Pathology Request Cover Letter, if specifically required by the pathology laboratory. Keep a copy of the site’s HIPAA Authorization and/or the original Authorization to Release Surgical Material in the participant’s ACRIN 6684 site file.

### 3.1.5 Pathology Report

A copy of the pathology report that describes the tissue(s) of interest should be attached to the Pathology Specimen Collection—Request Form. Keep the original pathology report in the participant’s 6684 site file.

### 3.1.6 Shipping Materials for Lending Pathology Laboratories

ACRIN 6684 sites should include all appropriate shipping materials in the request packet to facilitate shipment of specimens from pathology laboratories. The shipping materials to be included in the request packet are:

- Storage boxes for blocks (Fisher; dimensions 5” x 5” x 2”) if blocks are collected
- Storage boxes for slides (Fisher; dimensions 5 1/2” x 3 1/2” x 1 1/4”, holds 25 slides) if unstained sections are collected.
- Multi-purpose insulated bio-shippers (Thermosafe Bio-Shippers; dimensions 14” x 10” x 14”).
- Biohazard bags
- M3 carton sealing tape
- Styrofoam peanuts and/or bubble wrap.
- Cold Packs (to use for all shipments in climates with > 70°F temperature).
- Shipping labels to indicate: “Fragile—Handle With Care” and “Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650”

In the event that a clinical site cannot obtain the appropriate shipping materials, please contact, Rosa Medina, at ACRIN headquarters via e-mail at rmedina@acr-arrs.org. The e-mail should list the name of the person requesting the material, a list of materials needed, and the shipping address for shipment to the site. Make sure to put “Materials Requested, Study ACRIN 6684 and Site Number” in the e-mail ‘Subject’ line.

3.2 Pathology Laboratory Non-Response Follow-Up for Specimen Request

In the event that requested specimens are not received within three weeks of submitting the request, the ACRIN 6684 site coordinator will contact the local pathology department/laboratory and inquire if the laboratory received the request packet and if clarification or any further assistance is needed. If after two follow-up attempts, there is still no response, or if the pathology laboratory refuses to release any materials, the ACRIN 6684 site PI or designee will pursue negotiations with the pathology laboratory staff to gain access to these materials. The result of each follow-up effort will be documented on a hard copy Pathology Laboratory Non-Response Log: Request for Specimen(s) (Appendix VI). Non-response Logs should be stored in the participant’s chart.

4. Collecting Specimens at Study Centers

The lending pathology laboratory will receive the request packet and review the letter and accompanying form. If the pathology laboratory agrees to release the requested tissues, it will return the Pathology Specimen Collection—Request Form and the tissue to the ACRIN 6684 site. If the pathology laboratory is not willing to release the tissue, it should indicate the reason for refusal on the Pathology Specimen Collection—Request Form and fax or mail it back to the ACRIN 6684 site.

4.1 Receiving Specimens from Lending Pathology Laboratories

Receiving specimen materials at the ACRIN 6684 site involves review of both the completed Pathology Specimen Collection—Request Form and the specimens. The ACRIN 6684 site will implement the following procedures for receipt of specimens:

1. Verify that a completed Request Form was returned. If the form is missing or incomplete, request that a completed form be provided. Note: if a request form is not returned, fill out a “Note to File” and store it in the participants chart.
2. Verify that each specimen corresponds to the tissue(s) requested. If there are any discrepancies, contact the pathology laboratory and complete a Discrepancy Notification Form (Appendix VII).
3. Inspect each specimen for damage. If a block/slide is damaged, report the damage to the pathology department and request a replacement block/slide if available. Extremely damaged blocks (i.e. melted, severely punctured, cut in half, severely smashed) should be returned to the pathology lab.
4. The site coordinator should label each block/slide with the ACRIN 6684 ID label supplied by ACRIN HQ and attach identical labels to the Pathology Submission Form in the row that corresponds to that particular block/slide. The site coordinator should insure that any protected health information is de-identified prior to sending the specimens to the Pathology Core Facility.

4.2 Labeling and Storing Specimens from Lending Pathology Labs

For tracking purposes, each specimen and its associated forms should be labeled with the 6684 site number and case number. If a pathology laboratory identifier is visible on a block/slide after application of the 6684 ID label, supplied blank labels should be used as needed to mask the identifier. The trial-specific pathology specimen labels should be removed prior to eventual return to the lending pathology laboratories.

ACRIN will send pre-printed labels for all participant tissue blocks/slides.

The 6684 ID number printed on each label will uniquely identify each tissue block of a participant. The ID numbers have the
following format: (NNNN-NNN-NN)

- **NNNN**: four-digit ACRIN site number
- **NNN**: three-digit case number (starting at 01)
- **NN**: two-digit sequence number (starting at 01)

### **NNNN: four-digit ACRIN site numbers:**
- 4202 University of Pennsylvania
- 4205 Washington University Medical School
- 4221 University of Washington
- 4251 University of Alabama at Birmingham Medical Center
- 4282 Duke University Medical Center
- 4317 University of Southern California
- 4346 University of Wisconsin Hospital
- 4477 Mount Sinai Medical Center (4477)
- 4485 Massachusetts General Hospital
- 4493 University of California San Francisco

### **NN: three-digit case number (starting at 01):**
If multiple cases are entered into the study from a single ACRIN site, cases should be numbered consecutively, starting at 01. Each case will have the same ACRIN site number.

### **NN: two-digit sequence number (starting at 01):**
If multiple blocks are obtained for a single specimen, each will have the same ACRIN site number and case number followed by an incremental sequence number, starting at 01. Follow the instructions below to label the tissue blocks and to prepare blocks for shipping.

### **Labeling Slides of unstained sections:**
All slides should be labeled with the “NNNN-NNN-NN” format, with the first four digits being the ACRIN site number, the three digit case number and a two digit block number corresponding to the block from which the sections were cut. (For example, if slides for MGMT analyses (requiring >70% viable tissue) were cut from a different block than those for hypoxia/vasculature biomarkers (requiring viable tissue and necrosis), they should be labeled with two different block sequence numbers.)

### **Instructions:**
1. Attach the 6684 ID label to the side edge of the paraffin block cassette or slides.
2. Attach the duplicate label to the corresponding row on the Pathology Submission Form.
3. Use blank labels to cover personal identifiers elsewhere on the cassette/slides.
4. Place a copy of the pathology report in the biohazard bag form slot.
5. Place the cassette in the zip lock portion of the biohazard bag.
6. Place each bag in a 5” x 5” x 2” storage box. (Note: a box may fit 1-2 bagged specimens)
7. Place all slides in a 5 1/2” x 3 1/2” x 1 1/4” storage box (holds 25 slides).
8. Store in ambient temperature with cool ventilation until the tissue is shipped.
5. **Maintaining and Shipping Specimens to Pathology Core Facility**

The pathology specimens are preserved in paraffin. Prior to shipment, blocks or slides should be stored in a cool, dark container and be protected from excessive light and temperature to prevent deterioration of the wax and embedded tissue.

Shipping methods should take seasonal temperatures into account, and include the use of extra insulated packaging and a cooling agent (cold packs), as needed. The standard shipping package for a specimen should include the biohazard bag, placed in a storage box, which is then placed inside a foam-insulated shipping box (bio-shipper).

Specimens should be shipped by overnight FedEx to the Pathology Core Facility. The original Sample Submission Form (ACRIN website | Protocol 6684 Forms) and copies of the corresponding pathology report(s) should be included with the specimens. On the day of shipment (ship Monday to Wednesday only), the study coordinator will notify the Pathology Core Facility via e-mail (cnutt@partners.org) or Fax (617-726-5684: Attention Catherine Nutt) of the upcoming shipment. Include the estimated date of arrival and the FedEx tracking number.

**NOTE:** The subject line of the email/FAX should include the following so that the Pathology Facility staff can distinguish between blocks sent by ACRIN sites.

**ACRIN 6684 Specimen Block Shipment--Site [Name or ID].**

Upon receipt of specimens, the Pathology Core Facility will reconcile the materials and notify the 6684 study coordinator of missing specimens, damaged specimens, or any concerns to be addressed.

5.1 **Shipping Materials and Process**

The appropriate shipping materials for 6684 specimens are the following:

- Storage boxes for blocks (Fisher; dimensions 5” x 5” x 2”)
- Storage boxes for slides (Fisher; dimensions 5 1/2” x 3 1/2” x 1 1/4”, holds 25 slides)
- Multi-purpose insulated bio-shippers (Thermosafe Bio-Shippers; dimensions 14” x 10” x 14”)
- Biohazard bags
- Shipping labels
- M3 carton sealing tape.
- Styrofoam peanuts and/or bubble wrap.
- Cold Packs (to use for all shipments in climates with > 70°F temperature).
- Shipping labels to indicate: “Fragile—Handle With Care” and “Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650”

The packing process for shipments includes the following:

- Place a copy of the pathology report(s) for a single participant inside one biohazard bag, in the form slot, place the block(s) for that participant in the zip lock slot, then place the biohazard bag inside the white storage box (5” x 5” x 2”).
- For Slides, pack all slides in the slide storage box; place each corresponding pathology reports in its own biohazard bag, in the form slot.
- Pack the storage boxes containing the specimens in the shipping container box (14” x 10” x 14”).
- Place packing materials such as Styrofoam peanuts and/or bubble wrap in and around the storage boxes to prevent them from shifting during transit.
- Place the Pathology Submission Form(s) inside a zip-lock bag and place the bag inside the insulated shipping container on top of the filler material.
- Close the lids and seal the shipping container with tape.
- Maintain a copy of the transmittal log at the site.

5.2 **Labeling Shipping Containers**

Label each shipping container with the FedEx shipping label to include the following:

1. The study coordinator return address
2. The Pathology Core Facility address:

    Catherine Nutt  
    Molecular Pathology Unit  
    Massachusetts General Hospital  
    149 13th Street, Room 6014  
    Charlestown, MA 02129  
    E-mail: cnutt@partners.org  
    Phone: 617-643-2210  
    Fax: 617-726-5684

3. Notice: Fragile --- Handle with Care  
4. Notice: Diagnostic Specimens – Not restricted, Packed in Compliance with IATA Packing Instruction 650

5.3 Summary Shipping Task List
The following summarizes the tasks to complete by the site for a scheduled shipment:
- Prepare transmittal paperwork and retain copies at the ACRIN 6684 site.
- Send a notification e-mail | Fax to the Pathology Core Facility listing the items being shipped, including: the number of storage boxes, FedEx tracking number, total number of blocks in the shipment, and the expected date of arrival. Please note “ACRIN Specimen Block Shipment–Site [Name or ID].” in the e-mail | Fax ‘Subject’ line.
- Pack the blocks according to instructions above.
- Label each shipping container with the FedEx shipping label as well as the labels indicating fragile contents and diagnostic specimens.
- Maintain a copy of the transmittal log at the site.

6. Returning Loaned Specimens

   Loaned blocks will be mailed to the ACRIN 6684 site for return shipment to the originating pathology laboratory. Any slides obtained will not be returned to the sites. The slides will be used and destroyed per laboratory procedures.

   The site should contact the Pathology Core Facility to resolve any discrepancy or problems with return shipments. The ACRIN 6684 site is responsible for returning blocks within the timeframe specified by the lending pathology laboratory. If possible, loaned blocks can be batch-shipped to the lending pathology laboratories.

   Transmittals for returns to pathology laboratories are generated by the ACRIN 6684 site. Materials are packaged as described for specimen shipments to the Pathology Core Facility. ACRIN 6684 ID labels and blank masking labels should be removed prior to packaging for return.
APPENDIX I

AUTHORIZATION COVER LETTER TEMPLATE

<< Letterhead of 6684 Site >>

<< Date >>

<< Participant Name >>

<< Participant Address >>

Dear << Participant Title >> <<Participant Name >>,

Our records show that since the time you started with the ACRIN 6684, you have had a GBM related surgical procedure. We would like to obtain a small amount of the surgical material (also known as a pathology specimen) that was removed and preserved after your procedure. This will help future cancer research.

To allow us to obtain the material from the pathology lab, please sign the <<Authorization Form(s)>> included with this letter. We have enclosed two copies of the form. Please read, sign, and return one copy to us in the enclosed postage paid envelope. The other copy is for your records.

As you know, you have already given us consent for your involvement in ACRIN 6684, but because of important HIPAA laws that are designed to protect the privacy of your medical information, we are asking for this additional authorization to obtain a portion of the pathology specimen from the pathology lab.

If you have any questions about this request or the 6684 study, please call me or your 6684 study coordinator, << study coordinator >>, at << phone number>>. Thank you very much for your help with our continuing research.

Sincerely,

<< ACRIN 6684 Site PI >>

<< ACRIN 6684 Site PI Title >>

<< ACRIN 6684 Site >>

Enclosures: Authorization Form (two copies)

Self-addressed, stamped return envelope
APPENDIX II

Authorization To Release Surgical Material Template

<< Letterhead of ACRIN 6684 Screening Center >>

Authorization to Release Surgical Material & Related Health information that Identifies You for Research

Your signature below gives permission to staff at << Pathology Lab Name >> to release surgical material (also known as pathology specimen) and the related pathology report obtained during your diagnosis or treatment of GBM or related condition. The pathology specimen will be used for research in GBM cancer detection, prevention and treatment by the ACRIN 6684 in which you are a participant.

This authorization is required by law to protect your health information. The pathology specimen and pathology report will be released to your local ACRIN 6684 screening center, identified at the top of this form. Any identifying information attached to the pathology specimen and pathology report such as your name, specimen ID or medical record number will be removed or blanked out before being sent to the ACRIN 6684 Central Laboratory located at the Massachusetts General Hospital (Boston, MA) Pathology Core Facility. By signing this document, you authorize << Pathology Lab Name >> to release your pathology specimen and pathology report for this research. Your local ACRIN 6684 screening center will hold your health information in confidence, will use it only for study purposes, and will not release it to anyone other than the study team unless required by law. Only the screening center and Central Laboratory staff involved with ACRIN 6684 research will have access to your pathology specimen and pathology report for this research.

Your medical treatment will not be affected in any way based on your decision to sign or not sign this Authorization.

You may change your mind and revoke this Authorization at any time, except to the extent that any actions have already been taken based on this Authorization. To revoke this Authorization, contact your local ACRIN 6684 site or write to << Pathology Lab Name >>, << Pathology Lab Contact >>, << Pathology Lab Address >>. This authorization does not have an expiration date.

______________
Signature of Participant or
Participant’s Personal Representative

______________
Date Signed

______________
Printed Name of Participant or
Participant’s Personal Representative

______________
If Applicable, Description of
Personal Representative’s Authority
**APPENDIX III**

**PARTICIPANT NON-RESPONSE LOG: REQUEST FOR AUTHORIZATION**

<table>
<thead>
<tr>
<th>SECTION I: PARTICIPANT DATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACRIN 6684 Case #:</td>
</tr>
<tr>
<td>Participant initials:</td>
</tr>
<tr>
<td>Date of First Mailing:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECTION II: CALL RECORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of first mailing:</td>
</tr>
<tr>
<td>Date of last contact:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day: ___________</th>
<th>Outcome of Call</th>
<th>Reason for Refusal</th>
<th>Level of Refusal</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: / /2011</td>
<td>□ No Answer</td>
<td>□ Too Busy</td>
<td>□ Mild</td>
<td></td>
</tr>
<tr>
<td>Time of call: AM</td>
<td>□ Call Back</td>
<td>□ Not Interested</td>
<td>□ Firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Left Message</td>
<td>□ Call Back</td>
<td>□ Hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Already Sent</td>
<td>□ Other, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Initials:              | |

<table>
<thead>
<tr>
<th>Day: ___________</th>
<th>Outcome of Call</th>
<th>Reason for Refusal</th>
<th>Level of Refusal</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: / /2011</td>
<td>□ No Answer</td>
<td>□ Too Busy</td>
<td>□ Mild</td>
<td></td>
</tr>
<tr>
<td>Time of call: AM</td>
<td>□ Call Back</td>
<td>□ Not Interested</td>
<td>□ Firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Left Message</td>
<td>□ Call Back</td>
<td>□ Hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Already Sent</td>
<td>□ Other, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Initials:              | |

<table>
<thead>
<tr>
<th>Day: ___________</th>
<th>Outcome of Call</th>
<th>Reason for Refusal</th>
<th>Level of Refusal</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: / /2011</td>
<td>□ No Answer</td>
<td>□ Too Busy</td>
<td>□ Mild</td>
<td></td>
</tr>
<tr>
<td>Time of call: AM</td>
<td>□ Call Back</td>
<td>□ Not Interested</td>
<td>□ Firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Left Message</td>
<td>□ Call Back</td>
<td>□ Hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Already Sent</td>
<td>□ Other, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Initials:              | |

<table>
<thead>
<tr>
<th>Day: ___________</th>
<th>Outcome of Call</th>
<th>Reason for Refusal</th>
<th>Level of Refusal</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: / /2011</td>
<td>□ No Answer</td>
<td>□ Too Busy</td>
<td>□ Mild</td>
<td></td>
</tr>
<tr>
<td>Time of call: AM</td>
<td>□ Call Back</td>
<td>□ Not Interested</td>
<td>□ Firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Left Message</td>
<td>□ Call Back</td>
<td>□ Hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Already Sent</td>
<td>□ Other, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Initials:              | |

<table>
<thead>
<tr>
<th>Day: ___________</th>
<th>Outcome of Call</th>
<th>Reason for Refusal</th>
<th>Level of Refusal</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: / /2011</td>
<td>□ No Answer</td>
<td>□ Too Busy</td>
<td>□ Mild</td>
<td></td>
</tr>
<tr>
<td>Time of call: AM</td>
<td>□ Call Back</td>
<td>□ Not Interested</td>
<td>□ Firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Left Message</td>
<td>□ Call Back</td>
<td>□ Hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Already Sent</td>
<td>□ Other, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Initials:              | |
APPENDIX IV-A
PATHOLOGY REQUEST COVER LETTER TEMPLATE

<< Letterhead of 6684 Site >>

<<Date>>

Director, Pathology Department
(Hospital Name)
(Hospital Street Address)
(Hospital City, State, Zip code)

Dear Director of Pathology Department,

We are writing to request your participation in a pathology specimen collection for ACRIN 6684 Trial. <<ACRIN 6684 Site >> is collaborating with the National Cancer Institute (NCI) on this trial. The purpose of the study is to determine the to determine if FMISO PET imaging may be a useful predictive or prognostic marker in patients with GBM undergoing standard of care treatment with radiation and TMZ. These specimens offer great potential to increase our understanding of GBM and its genetic and environmental causes as well as for improving GBM prevention and treatment efforts.

The specimens collected from the ACRIN 6684 will be used to test for 5 biomarkers as well as determination of MGMT promoter methylation status. In addition, collected paraffin tissue blocks will have 1 section (5 μm thick) cut for H&E staining.

The ACRIN 6684 participant listed on the attached Request Form has given signed consent and authorization to collect these GBM related pathologies. These forms as well as a copy of the pathology report pertinent to this pathology material are provided.

The Pathology Request Form specifies the material we are requesting. For tumors, we are requesting the most representative specimen(s) of the tumor (include all representative histologies or grades) as well as tumor-free margin. A minimum 3-month loan period will be required by the Pathology Core Laboratory to process this specimen block. Ship the specimen(s) and copy of the Request Form using the enclosed self-addressed, postage paid shipping materials. Please advise us of any additional costs associated with this request for preserved tissue.

Thank you for your assistance with this research. If you have any questions, please call me or our study Coordinator: <<Site Study Coordinator>> at <<Phone Number>>.

Sincerely,

<<ACRIN 6684 Site PI>>

Enclosures: Pathology Request Form
Pathology report
Informed consent
Authorization Form for release of pathology specimens (if required)
APPENDIX IV-B
PATHOLOGY REQUEST COVER LETTER TEMPLATE

<<Letterhead of 6684 Site>>

<<Date>>

Director, Pathology Department
(Hospital Name)
(Hospital Street Address)
(Hospital City, State, Zip code)

Dear Director of Pathology Department,

We are writing to request your participation in a pathology specimen collection for ACRIN 6684 Trial. <<ACRIN 6684 Site>> is collaborating with the National Cancer Institute (NCI) on this trial. The purpose of the study is to determine the to determine if FMISO PET imaging may be a useful predictive or prognostic marker in patients with GBM undergoing standard of care treatment with radiation and TMZ. These specimens offer great potential to increase our understanding of GBM and its genetic and environmental causes as well as for improving GBM prevention and treatment efforts.

The specimens collected from the ACRIN 6684 will be used to test for 5 biomarkers as well as determination of MGMT promoter methylation status. In addition, collected paraffin tissue blocks will have 1 section (5 μm thick) cut for H&E staining.

The ACRIN 6684 participant listed on the attached Request Form has given signed consent and authorization to collect these GBM related pathologies. These forms as well as a copy of the pathology report pertinent to this pathology material are provided.

The Pathology Request Form specifies the material we are requesting. A minimum 3-month loan period will be required by the Pathology Core Laboratory to process this specimen block. If blocks can not be released, we request unstained sections on slides as outlined in the Pathology Request Form. A minimum of 20 5-μm thick (section areas >1cm²), unstained sections on chemoplus/plus slides will be acceptable. At least 10 slides are to be composed of mostly viable tumor cells (i.e. >70%) for MGMT testing. If tissue area is <1cm², an appropriate number of additional slides are requested in order to obtain an amount of tissue similar to that afforded by 10 5-μm thick sections at >1cm². Ten additional slides are requested for immunohistochemical analyses; these sections should ideally contain viable tumor tissue and areas of necrosis.

Ship the slides(s) and copy of the Request Form using the enclosed self-addressed, postage paid shipping materials. Please advise us of any additional costs associated with this request for preserved tissue.

Thank you for your assistance with this research. If you have any questions, please call me or our study Coordinator: <<Site Study Coordinator>> at <<Phone Number>>.

Sincerely,

<<ACRIN 6684 Site PI>>

Enclosures: Pathology Request Form
Pathology report
Informed consent
Authorization Form for release of pathology specimens (if required)
The ACRIN 6684 participant listed above reported resection of an operative GBM resection at your institution. We are requesting that you provide us with buffered formalin-fixed paraffin blocks of the tissue types listed below. For each block, please record the date of procedure, explicit block identification, and provide any additional comments as appropriate.

If no specimens will be sent, please indicate the reason below and fax to <<Site FAX>>.

[ ] NO specimens shipped        Reason__________________________________________________________

<table>
<thead>
<tr>
<th>Procedure Date</th>
<th>Tissue Type</th>
<th>Unique Block Identification</th>
<th>Comments about Block</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. How soon does material need to be returned to your facility (check box)? ☐ Permanent retention is permitted. ☐ Return in _____ months (3 months minimum required).

2. Please ship this form and the requested specimen(s) using the enclosed pre-paid packaging. OR, if no specimen can be sent, please indicate reason above and fax this form to: <<ACRIN 6684 Site Fax #, Attn: <<ACRIN 6684 Site Coordinator>>>.  
   <<Name of ACRIN 6684 Site>>  
   <<ACRIN 6684 Site Street Address>>  
   <<City, State, Zip code>>

This report contains data protected by HIPAA. Distribute only to authorized staff, and store and dispose in a proper manner.
APPENDIX V-B

Participant Name:
Date of Birth:
Medical Record #:

PATHOLOGY SPECIMEN COLLECTION (SLIDE REQUEST FORM)

The ACRIN 6684 participant listed above reported resection of an operative GBM resection at your institution. We are requesting that you provide us with unstained slide sections. For each slide, please record the date of procedure, explicit slide identification, and provide any additional comments as appropriate. If blocks can not be released by your institution, we request slides of unstained sections as outlined below.

If no specimens will be sent, please indicate the reason below and fax to << Site FAX >>.

[ ] NO specimens shipped

Reason

<table>
<thead>
<tr>
<th>Procedure Date</th>
<th>Tissue Type</th>
<th>Unique Slide Identification</th>
<th>Comments about Slides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Please ship this form and the requested specimen(s) using the enclosed packaging. OR, if no specimen can be sent, please indicate reason above and fax this form to:

<<ACRIN 6684 Site Fax #, Attn: << ACRIN 6684 Site Coordinator>>>,
<<Name of ACRIN 6684 Site>>
<<ACRIN 6684 Site Street Address>>
<<City, State, Zip code>>

This report contains data protected by HIPAA. Distribute only to authorized staff, and store and dispose in a proper manner.
### Instructions:
The Non-response Log should be used to document effort to obtain pathology tissue from a pathology lab. Guidelines for follow-up effort are included in the Pathology Tissue Process Manual section 3.2.

### Section I: Participant Data

<table>
<thead>
<tr>
<th>ACRIN ACRIN 6684 case #</th>
<th>Pathology Lab Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACRIN ACRIN 6684 case #</td>
<td>Pathology Lab Address</td>
</tr>
<tr>
<td>Participant Initials:</td>
<td>Pathology Lab Address</td>
</tr>
</tbody>
</table>

### Section II

<table>
<thead>
<tr>
<th>Pathology Lab Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Person at Lab</td>
</tr>
<tr>
<td>Phone</td>
</tr>
<tr>
<td>Fax</td>
</tr>
</tbody>
</table>

### Section III: Call Record

<table>
<thead>
<tr>
<th>Date of first mailing:</th>
<th>Outcome of Call</th>
<th>Reason for Refusal</th>
<th>Level of Refusal</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□ No Answer</td>
<td>□ Too Busy</td>
<td>□ Mild</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Call Back</td>
<td>□ Not Interested</td>
<td>□ Firm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Left Message</td>
<td>□ Call Back</td>
<td>□ Hostile</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Already Sent</td>
<td>□ Other, specify:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Refusal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day: _____________</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date: <em><strong><strong>/</strong></strong></em>/2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of call: _______</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM: _______ PM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initials:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Date of last contact: | |
|-----------------------|---
| Day: _____________     | |
| Date: _____/_____/2011 | |
| Time of call: _______  | |
| AM: _______ PM        | |
| Initials:             | |

| Day: _____________     | |
| Date: _____/_____/2011 | |
| Time of call: _______  | |
| AM: _______ PM        | |
| Initials:             | |

| Date: _____/_____/2011 | |
| Time of call: _______  | |
| AM: _______ PM        | |
| Initials:             | |

| Day: _____________     | |
| Date: _____/_____/2011 | |
| Time of call: _______  | |
| AM: _______ PM        | |
| Initials:             | |
APPENDIX VII
ACRIN 6684 PATHOLOGY SPECIMEN COLLECTION
DISCREPANCY NOTIFICATION

TO: ____________________________________________
FROM: ____________________________________________
DATE: ____________________________________________

SUBJECT: Problem with 6684 specimen shipment dated: __________________________

SPECIMEN ID: ____________________________________________

PROBLEM DESCRIPTION: ____________________________________________

PROBLEM RESOLUTION: ____________________________________________

DATE OF RESOLUTION: ____________________________________________