

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6660

WHOLE-BODY MRI IN THE EVALUATION OF PEDIATRIC MALIGNANCIES

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INDEX

Schema3

1.0 Abstract5

2.0 Background and Significance.....5

3.0 Specific Aims13

4.0 Study Overview13

5.0 Participant Selection14

6.0 Site Selection15

7.0 Online Registration System.....16

8.0 Data Collection and Management17

9.0 Data Collection Forms.....22

10.0 Image Submission24

11.0 Imaging Assessment.....25

12.0 Image Interpretation28

13.0 Confirmatory Studies for Positive Finds on Whole-Body MRI and FDG-PET30

14.0 Follow Up.....30

15.0 Proof of Truth in Diagnosis.....31

16.0 Adverse Event Reporting31

17.0 Statistical Considerations **REMOVED FROM WEB VERSION**35

18.0 Ethical Considerations.....40

19.0 Institutional Audits42

References46

Appendix I: Sample Consent Forms.....48

Appendix II: Eligibility Checklist.....57

Appendix III: Participating Institutions60

Appendix IV: Specific Imaging Protocols (CT/MRI/Scintigraphy/FDG-PET)62

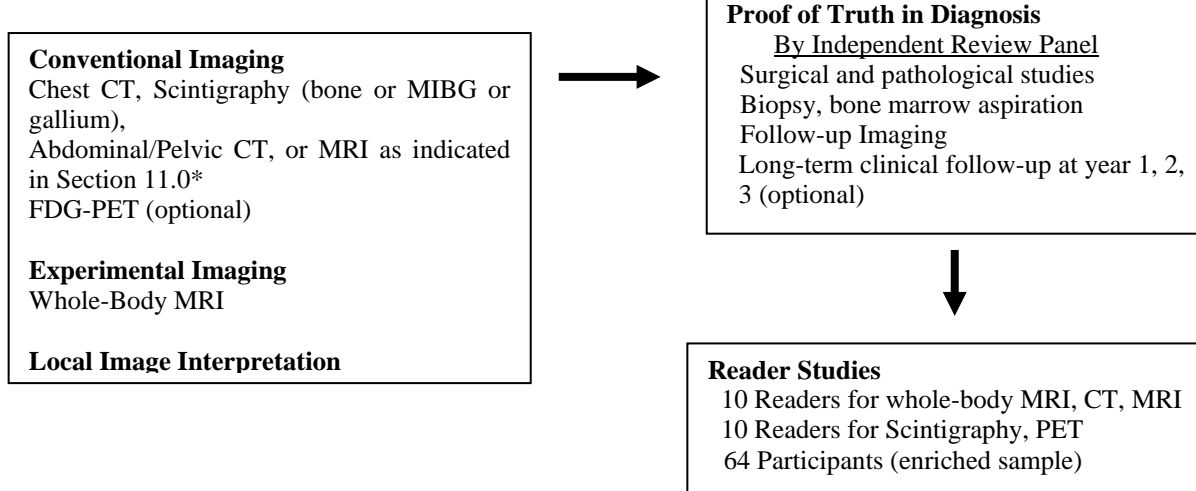
Appendix V: Radiopharmaceutical Dosimetry63

Appendix VI: Staging Systems65

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SCHEMA

REGISTRATION



*NOTE: Conventional Imaging tests will follow section 11.0 and are disease type specific.

Eligibility (See Section 5.0 for details)

- Male or female participants.
- Age 21 years or younger.
- Participants with proven rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS) Ewing's sarcoma Family of Tumors (ESFT), neuroblastoma, Hodgkin's disease, or non-Hodgkin's lymphoma, and other sarcomas (except for osteosarcoma), or newly diagnosed mass strongly suspected to represent rhabdomyosarcoma, Ewing's sarcoma Family of Tumors (ESFT), neuroblastoma, Hodgkin's disease, or non-Hodgkin's lymphoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), and other sarcomas (except for osteosarcoma).
- Participants with prior CT studies, conventional MR, FDG-PET, bone scintigraphy, MIBG scintigraphy, or gallium scintigraphy performed at the site or at outside institutions may be included in this protocol if these studies were performed with the same technical standards specified in this protocol (see Appendix IV for radiologic examination).
- Participants with prior biopsies or operative procedures performed at the site or at outside institutions or prior to any therapeutic treatment (radiation therapy or chemotherapy) may be included in this protocol if the procedure is performed within 2 months of imaging studies and the pathologic diagnosis is verified in a written report either by a prior pathologist or a local site pathologist.
- Participant's parents (if participant is under 18) or the participant (if participant is 18 years or older) must willingly give written informed consent prior to the start of the study.
- All required imaging examinations (CT, MRI, Bone Scintigraphy, MIBG Scintigraphy, and Gallium Scintigraphy) must be performed within 14 calendar days of each other and within 2 months of any diagnostic or operative procedure. Prior to treatment, whole-body MRI and PET (if PET is being done) must be performed, as well as at least one nuclear medicine test.

In addition, a chest CT must be performed prior to treatment, except for those participants with neuroblastoma. In participants with neuroblastoma, CT or MR of the primary must be performed prior to treatment. Chest CT is optional for those participants. Bone scintigraphy or MIBG scintigraphy will be acquired in participants with neuroblastoma. Bone scintigraphy will be performed in participants with rhabdomyosarcoma and other sarcomas. Gallium scintigraphy may be acquired in participants with lymphoma, but it is not required if PET is performed.

- Participants with contraindications for MRI (including cardiac pacemakers or intracranial vascular clips) or CT, or who have had a previous malignancy, or osteosarcoma, or CNS primary tumor, are excluded.
- Participants who are pregnant or nursing are excluded.

Required Sample Size: Participants will be enrolled until 32 eligible, confirmed positives evaluable for the primary endpoint have been accrued. We are 90% certain that the total sample size will be at most 226 participants. We expect this to include 45 neuroblastoma participants, 54 rhabdomyosarcoma participants, 27 other sarcoma participants, and 100 lymphoma participants.

Reader Studies: 10 pediatric radiologists, 10 nuclear medicine specialists.

1.0 ABSTRACT

Small cell tumors in childhood present significant challenges in oncologic imaging—specifically in determining extent, which is important in planning treatment and predicting outcome. Treatment protocols involving targeted drug delivery using monoclonal antibodies or agents such as metaiodobenzylguanidine (MIBG) are currently being developed. If the results of these treatment protocols are to be accurately assessed, the ability of pre-treatment imaging studies to stage tumors must be known. Computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy are important techniques in the staging and management of pediatric solid tumors (1-3). However, the use of MRI to scan the entire body for staging of pediatric tumors has been limited due to long imaging times (typically 60 to 90 minutes), the need for sedation, and high cost.

Whole-body MRI techniques hold promise for diagnosing and staging tumors. Recent work has shown that whole-body MRI techniques can be performed in less than 10 to 15 minutes in adult patients, and that such a technique can be useful in detecting metastases (4-9). In addition, a number of studies in adults have demonstrated the utility of positron emission tomography (PET) with [¹⁸F] fluoro-2-deoxy-D-glucose (FDG) for detection of metastatic disease in a variety of tumors (10-11). FDG-PET is also emerging as an important imaging tool in children, but larger series are needed to evaluate its accuracy in detecting metastatic disease (12-15). Therefore, this study was designed to determine the accuracy of whole-body MRI and FDG-PET for detecting metastatic disease in common primary tumors in children.

Participants under the age of 21 with common childhood cancers will undergo whole-body MRI using 2 sequences, and may also undergo FDG-PET. Imaging results will be correlated with results from surgery and bone marrow aspiration or biopsy, and compared with conventional imaging techniques for staging these cancers. The clinical status of the participant at years 1, 2, and 3 from study enrollment may be ascertained for possible subsequent exploratory analyses regarding the clinical impact of the research imaging.

The primary purposes of this study include:

- 1.1** To establish non-inferior diagnostic accuracy of whole-body MRI (combination of turbo STIR [short-tau inversion-recovery] and out-of-phase imaging) compared with conventional imaging (the combination of chest CT, scintigraphy [bone, gallium, MIBG, or optional FDG-PET] and abdominal/pelvic CT/MRI as indicated) for detecting distant metastases for use in staging common pediatric tumors.
- 1.2** To determine the incremental benefit in accuracy of adding out-of-phase (OOPS) T1 weighted gradient recalled echo imaging to turbo STIR for detecting distant disease.
- 1.3** To obtain preliminary data concerning the relative accuracies of FDG-PET, whole-body MRI, and a combination of FDG-PET and whole-body MRI in detecting Stage IV disease.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Clinical Assessment

Accurate assessment of the extent of malignant tumors in children is an important clinical goal, as the presence of widespread or metastatic disease substantially

alters prognosis and therapy. Rhabdomyosarcoma, primitive neuroectodermal tumor (PNET), and Ewing's sarcoma are the most common soft-tissue malignancies that occur in the pediatric population. They have the potential to metastasize to multiple areas, including bone and bone marrow. Neuroblastoma is the most common solid tumor of childhood. It arises from sympathetic nerve tissue. Distant metastases are to bone, bone marrow, lymph nodes, and liver. Lymphoma is a hematologic malignancy that is one of the most common tumors in children. Hodgkin's disease primarily involves nodal groups, but it can spread to solid organs and bone marrow. Non-Hodgkin's disease typically involves extranodal sites, including solid organs and bone marrow. Obviously, accurate imaging of children with malignancy is critical to staging and treatment planning.

2.1.1 *Rhabdomyosarcoma*

Rhabdomyosarcoma is the most common soft tissue malignancy and the third most common non-central nervous system tumor in childhood. According to data from the Surveillance, Epidemiology, and End Results (SEER) program, in children through 19 years of age, the incidence of rhabdomyosarcoma was 4.7 diagnoses per million children in the population per year during 1993-1999, comprising 2.9% of all the childhood cancers (16). The two primary histologic variants of rhabdomyosarcoma are embryonal and alveolar. Most rhabdomyosarcomas arise in the head and neck, retroperitoneum and genitourinary tract, and extremities. Tumors in the head and neck can present as a mass lesion, or with proptosis and ophthalmoplegia. Tumors in the genitourinary tract can present with urinary obstruction or a pelvic mass. Rhabdomyosarcomas of the extremities produce pain and tenderness at the involved site. Approximately 16% of patients with rhabdomyosarcoma have distant metastases at presentation (17). The principal sites of distant metastases are lymph nodes, lung, liver, bone marrow, and brain (18-20).

The principal prognostic factors associated with this neoplasm include age of the patient, primary tumor site, histologic type, cellular DNA content, and stage at the time of disease presentation. Treatment of rhabdomyosarcoma consists of surgery, radiation, and chemotherapy.

2.1.2 *Ewing's Sarcoma Family of Tumors (ESFT)*

Ewing's sarcoma is a small round cell tumor of bone usually occurring in the first two decades of life. According to data from the SEER program, the annual incidence rate of Ewing's sarcoma was 2.8 diagnoses per million children in the population per year during 1993-1999 (16). Ewing's sarcoma family of tumors includes Ewing's Sarcoma, peripheral primitive neuroectodermal tumors, and desmoplastic round cell tumors. Together, they comprised 5.8% of all childhood cancers. Histologically, these tumors are now known to originate from the neural crest. This tumor type is characterized by a neural immunophenotype or by neural differentiation on ultrastructural examination. Pathologic features that impact prognosis include proliferative indices and the degree of differentiation.

Patients with Ewing's Sarcoma Family of Tumors commonly present with pain, palpable mass, fracture, or fever. The site of origin is evenly split between the central axis and the extremities. On initial presentation, 15%-31% of patients will have overt metastases (21). Common sites of metastatic disease include the lung and bone marrow. The standard laboratory evaluation for Ewing's sarcoma and peripheral PNET includes biopsy of the lesion, LDH, catecholamine levels (if neuroblastoma is in the differential), and marrow biopsy. Treatment of these tumors consists of surgery, radiation, and chemotherapy.

2.1.3 Neuroblastoma

Neuroblastoma is the most common malignant abdominal tumor in children, with an annual incidence rate of 8.3 diagnoses per million children in the population per year during 1993-1999, accounting for 5.2% of all childhood cancers (16). The prevalence of neuroblastoma is about 1 per 7,000 live births, and there are about 550 newly diagnosed cases of neuroblastoma in the United States annually (20). Neuroblastomas arise from the adrenal medulla, ganglia, paraganglia, or the organ of Zuckerkandl. The majority of neuroblastomas (65%) are intraabdominal. However, neuroblastoma can arise in the cervical and thoracic regions. Common presenting complaints of neuroblastoma include abdominal pain, fullness, abdominal mass, lower extremity edema, anorexia, vomiting, bone or back pain, dysphagia, respiratory distress, superior vena cava syndrome, and Horner's syndrome. The survival for all children diagnosed with neuroblastoma varies with the patient's age at diagnosis, primary site and extent of disease, tumor histology, biochemical characteristic (VMA: HVA levels, serum ferritin levels, LDH, neuron specific enolase), cytology (ploidy, N-myc amplification, structural abnormalities), and immunologic status.

Traditionally, CT and MRI have been the standard imaging tests for local staging of the primary tumor. Bone scintigraphy and MIBG scintigraphy are the primary imaging tests for detecting bone marrow/bone involvement. Recently, Siegel et al (3) showed that MRI alone is superior to CT and equivalent to CT combined with bone scintigraphy for staging of neuroblastoma. About 60% of children with neuroblastoma will have metastatic disease at the time of clinical presentation. The definitive diagnosis of neuroblastoma is made by biopsy or bone marrow aspiration.

The treatment modalities used in neuroblastoma include surgery, chemotherapy, and radiation therapy. Staging is crucial in determining optimal therapy. Therapeutic modalities that are currently under investigation include radionuclide therapy with ¹³¹I-MIBG, autologous bone marrow infusion, immunotherapy, anti-angiogenesis therapy, and new chemotherapeutic agents.

2.1.4 Lymphoma

Both Hodgkin's disease and non-Hodgkin's lymphoma occur in children. The annual incidence rates for children through age 19 are 12.5 per million for Hodgkin's disease, and 10.5 per million for Non-Hodgkin's lymphoma, during the period 1993-1999; together, they comprise 14.3% of all childhood cancers (16). The expected number of new cases of Hodgkin's disease and non-Hodgkin's lymphoma per year are approximately 400 and 770, respectively.

The most common clinical presentation of Hodgkin's disease in childhood is painless cervical or supraclavicular adenopathy. The disease spreads by means of involvement of contiguous lymph node groups and in advanced disease may involve extralymphatic organs or tissues. Stage IV disease occurs in 10 to 15% of children and adolescents at presentation (22). The treatment modalities are chemotherapy and radiation therapy.

There are three major histologic types of non-Hodgkin's lymphoma: lymphoblastic lymphoma; small noncleaved cell lymphoma (including Burkitt's lymphoma), and large-cell lymphoma. Symptoms vary with the histologic type. Of those with small non-cleaved cell lymphoma, about 8% have advanced disease. Of those with lymphoblastic lymphoma, about 10% have advanced disease (23).

2.2 The Role of Imaging

The staging of small cell tumors requires radiologic tests and bone marrow aspiration. The choice of the most appropriate treatment protocol for an individual patient depends on non-operative methods, including imaging tests, for provision of staging information. Thus, staging is a major area of application for diagnostic imaging tests in patients with malignant small cell neoplasms. The principal morphologic parameters that influence disease control and patient survival are the site of tumor, local extension, and hematogenous dissemination (chiefly to bone or to bone marrow).

The standard imaging tests have included MRI, scintigraphy, and CT to determine the local extent of the primary tumor and to locate distant metastases. Conventional MRI is used to evaluate the local extent of the primary soft-tissue tumor. Bone scintigraphy is used to search for distant skeletal metastases. CT is used to evaluate suspected bone involvement and distant visceral metastases.

The conventional MRI techniques are limited by long imaging times in the range of 45 minutes to one hour. This is particularly problematic in the pediatric population, where such long imaging times often require the use of sedation, which has well documented risks. Recent advances in MRI, particularly the development of fast imaging sequences such as turbo-spin echo, echoplanar imaging, and fast gradient-echo techniques, have significantly reduced imaging time without compromising image quality significantly. These advances have led to many novel clinical applications of MRI techniques (4-9).

The potential of whole-body MRI led us to propose a study in which MRI is compared to other imaging tests, CT in particular, using pathologic specimens and

bone marrow sampling toward providing the reference standard, or the truth in diagnosis. If whole-body MRI can accurately detect distant metastases, these techniques may substitute for the combination of CT and scintigraphy and may provide a “one stop shop” for the staging of solid small cell tumors in the pediatric population.

Most recently, FDG PET has been used to investigate a variety of types of tumors in adults, including brain, lung, breast, colon, and musculoskeletal tumors (10-11). To date, few studies have evaluated the role of FDG PET in staging pediatric tumors (12-15). Since FDG PET is emerging as a promising test in staging malignancy, we believe that it is necessary to include this technique in our project, which addresses staging of pediatric tumors. Since the number of imaging centers that have PET scanners is limited, we have included FDG PET imaging as an optional arm of this protocol.

2.2.1 *Metastases: MRI*

Horvath et al (4) showed in a recent study that total body echoplanar imaging was an effective means of assessing spread from breast cancer metastases. Disease was correctly staged in 18 out of 20 patients using whole-body MRI, whereas conventional imaging detected metastases in only 15 out of 20 patients. Limitations of this study include a small sample size, and failure to employ sequences such as fast gradient-echo and STIR sequences, which eliminate many of the artifacts inherent to echoplanar imaging such as susceptibility artifact at air/tissue interfaces and geometric distortion secondary to magnetic field inhomogeneities.

Layer et al (7) showed, in a study of 52 patients with small cell lung cancer or breast cancer, that conventional pelvic and spine MRI was able to detect bone metastases from small cell lung cancer better than marrow biopsy and bone scintigraphy. In equivocal cases, these authors used chemical-shift imaging spectroscopic data and contrast enhancement. The reference standard in this study consisted of clinical and radiologic follow-up at 12 months, autopsy, or image-guided biopsy in those cases where the diagnosis was not made by unilateral iliac crest biopsy. MRI showed evidence of metastatic disease from small cell lung cancer in 25 patients, whereas bone scintigraphy was positive in only seven patients, and iliac crest biopsy showed evidence of metastatic disease in six patients. There was only one false-positive examination by MRI. However, in the patients with breast cancer, this study showed MRI to be not significantly different as compared with a combination of bone scintigraphy and iliac crest biopsy. Limitations of this study include the failure to employ whole-body MRI techniques and to study faster imaging techniques. Furthermore, T2-weighted sequences were not obtained in all cases.

Eustace et al (6) showed in a study of 25 patients with known or suspected skeletal metastases that whole-body STIR was more sensitive than bone scintigraphy. This study included six patients with breast cancer, ten patients with lung cancer, four patients with prostate cancer, one patient with nasopharyngeal cancer, two patients with cervical cancer, one patient

with lymphoma, and one patient with laryngeal cancer. The reference standard in this case was clinical follow-up at least one year after the imaging test, biopsy, autopsy, or dedicated CT/MRI. Overall, MRI had a sensitivity of 96.5% and a specificity of 100%, while bone scintigraphy had a sensitivity of 72% and a specificity of 98%. Limitations of this study include the small sample size of each particular tumor type and a failure to use MRI techniques other than whole-body STIR.

Walker et al (9) performed a study of 17 patients with biopsy-proven breast cancer, comparing STIR sequences with conventional imaging in the detection of central nervous system (CNS), hepatic, and bone metastases. Eleven of 17 patients had bone metastases by both STIR and bone scintigraphy. One patient was found to have false-positive bone scintigraphy and one patient had false-negative bone scintigraphy. Four patients had negative results on both imaging tests, which correlated to clinical outcome at one year. In two patients, whole-body STIR showed five lesions of the liver, while CT found only three of the five lesions. Both patients were subsequently found to have biopsy-proven metastases on follow-up. Though promising, this study was limited by the small sample size.

MRI has been shown to be more sensitive for the detection of skip lesions in Ewing's sarcoma than bone scintigraphy. Davies et al (24) studied retrospectively 82 patients with Ewing's sarcoma. Three patients had skip lesions detected by MRI that were not seen with bone scintigraphy. However, bone scintigraphy was performed at outside institutions in all cases with no uniformity in technique or interpretation. Furthermore, this study did not compare MRI with CT, nor was MRI used to examine more distant sites of metastases.

Data on MRI for detecting distant metastases to bone or bone marrow in children are extremely sparse. Results from the recent Radiologic Diagnostic Oncology Group (RDOG) study have shown that conventional MRI is an effective imaging technique for detecting marrow metastases in the spine, pelvis and proximal femora in children with neuroblastoma (3). A limitation of the RDOG study was that imaging did not screen the entire body.

Daldrup-Link (25) compared FDG-PET, whole-body MRI and bone scintigraphy for the detection of bone metastases in 39 children and young adults with a variety of tumors, including Ewing sarcoma, osteosarcoma, lymphoma, rhabdomyosarcoma, melanoma, and Langerhan's cell histiocytosis. All patients underwent T1-weighted MRI sequences and 10 underwent both T1-weighted and STIR sequences. Twenty-one patients had 51 bone metastases. Sensitivity for metastasis detection was 90% for FDG-PET, 82% for whole-body MRI, and 71% for bone scintigraphy. FDG-PET had more false-positive results than scintigraphy or MRI when the diagnosis of metastatic disease was based on the presence of an abnormality on both the STIR MRI sequence and the T1-weighted sequences. MRI had the highest number of false-positive diagnoses when

the diagnosis of bone metastases was based on the STIR sequence only. Limitations of this study were the small sample size of each particular tumor type and the failure to employ faster MRI techniques in the entire population.

Most recently, Mazumdar et al (26) compared both STIR imaging and T1-weighted MR imaging with CT and scintigraphy for detection of metastases in seven children with small cell tumors, including rhabdomyosarcoma, Ewing sarcoma and neuroblastoma. MRI correctly identified metastases in all seven patients. Three patients had bone marrow metastases and four patients had distant metastases (1 pleural, 1 renal, and 2 retroperitoneal). Turbo-STIR detected more marrow metastases than T1-weighted sequences in the patient with neuroblastoma and more marrow lesions than scintigraphy in one patient with rhabdomyosarcoma. Limitations of this study were the small sample size of each particular tumor type.

For the whole-body MRI part of the current study, patients will undergo both out-of-phase (OOPS) T1 weighted gradient recalled echo scanning and turbo STIR imaging. The OOPS sequence has been selected because it affords a fast effective T1-weighted examination, which is particularly important in the evaluation of marrow disease (27). Disler et al used T1 weighted spin echo in-phase-scanning (IPS) and OOPS to detect skeletal metastases. The role of IPS was to differentiate between fat and metastatic disease. If there was bright signal in the same location on the IPS and OOPS, the lesion represented fatty marrow. If there was dark signal on the IPS and a bright signal on the OOPS, the lesion was likely to be a metastasis. In our study, we propose to substitute a turbo STIR sequence for the IPS sequence. The turbo STIR sequence will allow evaluation of metastases in solid organs as well as in bone marrow. The combination of OOPS and turbo-STIR will also allow differentiation of metastases from red and yellow marrow. Fatty marrow will be bright on OOPS and dark on turbo STIR. Mixed or hematopoietic marrow will be dark on OOPS and intermediate on STIR. Metastases will be bright on both sequences.

2.2.2 *Metastases: FDG-PET*

In contrast to the dependence primarily on anatomic imaging features, PET depends upon the metabolic characteristics of a tissue for the detection of disease. It is known that a biochemical feature of malignant tissue is its high rate of glycolysis. This can be assessed by PET with the glucose analogue FDG. FDG competes with glucose for uptake into the cell, where it accumulates after phosphorylation. The amount of FDG accumulation over a fixed period is therefore proportional to the rate of cellular glucose metabolism and malignant potential of the tissue.

There are preliminary data to suggest an advantage of FDG-PET in the staging of common pediatric tumors.

Shulkin et al (15) assessed the uptake of FDG by PET in common and uncommon malignant tumors in children. Twenty-two pediatric patients

with known or suspected malignancies (27 scans) underwent FDG PET. Tumor uptake of FDG was detected in 17 of 21 patients with malignant disease. In one patient with Ewing's sarcoma, FDG PET showed two foci of metastatic disease not evident on bone scintigraphy. The authors surmised that many solid tumors in children accumulate FDG and that PET has the potential to be useful in the study of tumors in children. The limitations of this study were the small sample size of each particular tumor and the limited number of patients with distant metastases.

Newman et al (13) prospectively compared the accuracy of FDG-PET imaging of the chest and abdomen to that of CT in 16 patients with lymphoma (11 with non-Hodgkin's lymphoma and five with Hodgkin's disease). Fifty-four foci of abnormal uptake were detected with PET in 13 patients. Forty-nine corresponding sites of lymphadenopathy and/or masses were detected with CT. All sites of adenopathy seen at CT were detected at PET. Three patients with Hodgkin's disease had negative findings at abdominal PET, CT, and subsequent staging laparotomy. FDG uptake was comparable for both the low- and intermediate-grade lymphomas. The results indicated excellent accuracy for FDG-PET imaging of thoraco-abdominal lymphoma. All grades of non-Hodgkin's lymphoma were successfully imaged with FDG-PET. Study limitations were the relatively small and exclusively adult patient population and the outdated CT equipment.

Kushner et al (12) evaluated the role of FDG-PET in the follow-up of 51 patients with high-risk neuroblastoma. The results of PET were compared with those of I-123 or I-131 MIBG scintigraphy, bone scintigraphy, CT, and bone marrow examinations. The minimum number of tests sufficient to detect neuroblastoma was determined. Of 40 patients who were not in complete remission, only 1 (2.5%) had neuroblastoma that would have been missed had a staging evaluation been limited to PET and bone marrow studies. PET was equal or superior to MIBG scintigraphy for identifying neuroblastoma. FDG skeletal uptake was diffusely increased with extensive or active marrow disease but faint or absent with minimal or nonprogressing disease. Cranial vault lesions were not seen well by PET. Though promising, this study was limited by the small population (n=4) of patients with newly diagnosed neuroblastomas.

Shulkin et al (14) compared FDG-PET and MIBG scintigraphy in 17 patients with known or suspected neuroblastoma. Seven patients underwent imaging at initial diagnosis, prior to treatment. Histologic confirmation of bone marrow metastases was found in 6 of these 7 patients. Tumor uptake of FDG was detected in 6 of 7 newly diagnosed patients. Neuroblastomas and their metastases avidly concentrated FDG prior to chemotherapy or radiation therapy. Uptake after therapy was variable. The usefulness of this study is limited by the small sample size.

2.2.3 Significance

The preliminary MRI and PET data involve either small numbers of patients or reflect studies that are methodologically suboptimal. In addition, there are no definitive data reported concerning false-positive PET findings. There is a need for a prospective multicenter trial that assesses the clinical contribution of whole-body MRI and FDG-PET.

Our proposed study will evaluate the role of whole-body MRI, with PET as an optional arm, in staging common tumors in children.

3.0 SPECIFIC AIMS

3.1 Primary Aim

To establish non-inferior diagnostic accuracy of whole-body MRI (combination of turbo STIR and out-of-phase imaging) compared with conventional imaging (the combination of chest CT, scintigraphy [bone, gallium, MIBG, or optional FDG-PET] and abdominal/pelvic CT/MRI as indicated) for detecting distant metastases for use in staging common pediatric tumors.

3.2 Secondary Aims

- 3.2.1** To determine the incremental benefit in accuracy of adding out-of-phase (OOPS) T1 weighted gradient recalled echo imaging to turbo STIR for detecting distant disease.
- 3.2.2** To obtain preliminary data concerning the relative accuracies of FDG-PET, whole-body MRI, and a combination of FDG-PET and whole-body MRI in detecting Stage IV disease.
- 3.2.3** To assess the effects of multiple factors including cancer type, site of primary tumor, and patient age on diagnostic accuracy of whole-body MRI.
- 3.2.4** To examine the interobserver variability associated with interpreting whole-body MRI exams for detecting distant metastases.

4.0 STUDY OVERVIEW

All eligible participants will undergo conventional MRI, CT, and scintigraphy (bone, MIBG, or gallium) as well as the experimental whole-body MRI sequences. FDG-PET imaging is optional; however, if it is performed for lymphoma participants they will not be required to undergo scintigraphy. Proof of truth in diagnosis, which will serve as the reference standard, will be established by an independent review panel. This panel will base their diagnosis of stage on surgical and pathological proof, biopsy and bone marrow aspiration and/or follow-up imaging tests including, but not limited to, scintigraphy, CT, and MRI. Long-term clinical follow-up may be obtained at years 1, 2, and 3 from study enrollment. Accuracy will be evaluated based on local interpretations of the imaging tests; a subsequent reader study will be used to achieve sufficient statistical power to enable establishment of non-inferiority of whole-body MRI to conventional imaging for detecting distant metastases. Readers will comprise 10 radiologist-nuclear medicine specialist pairs, interpreting conventional imaging examinations independently and then jointly. A group of 10 pediatric radiologists will interpret abdominal/pelvic CT or MRI, chest CT, and whole-body MRI images on an enriched sample of 64 participants; a

second group of 10 nuclear medicine specialists will interpret bone, MIBG and gallium scintigraphy, and PET studies on the same sample. The primary objective of this study is establishment of non-inferior diagnostic accuracy of whole-body MRI compared with conventional imaging in detection of distant metastases of pediatric tumors, based on the reader study.

5.0 PARTICIPANT SELECTION

The referring clinician or research associate (RA) will identify potentially eligible participants. If the patient is eligible, the goals of the study and requirements for follow-up examinations (through 6 months after study enrollment) will be explained. Long-term follow-up is optional. Parental informed consent (for participants under age 18) or participant informed consent (for participants ages 18-21) will then be obtained by the principal investigator or a representative.

5.1 Inclusion Criteria

- 5.1.1** Male or female participants
- 5.1.2** Participants must be 21 years or younger.
- 5.1.3** Participants with proven rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), Ewing's sarcoma Family of Tumors (ESFT), neuroblastoma, Hodgkin's disease, or non-Hodgkin's lymphoma, and other sarcomas (except for osteosarcoma), or newly diagnosed mass strongly suspected to represent rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), Ewing's sarcoma Family of Tumors (ESFT), neuroblastoma, Hodgkin's disease, or non-Hodgkin's lymphoma, and other sarcomas (except for osteosarcoma).
- 5.1.4** Participants with prior CT studies, conventional MR, FDG-PET, bone scintigraphy, gallium scintigraphy, or MIBG scintigraphy performed at the site or at outside institutions may be included in this protocol if these studies were performed with the same technical standards specified in this protocol (see Appendix IV for radiologic examinations).
- 5.1.5** Participants with prior biopsies or operative procedures performed at the site or at outside institutions or prior to any therapeutic treatment (radiation therapy or chemotherapy) may be included in this protocol if the procedure is performed within 2 months of imaging studies and the pathologic diagnosis is verified in a written report either by a prior pathologist or a local site pathologist.
- 5.1.6** Participant's parents (if participant is under 18) or the participant (if participant is 18 years or older) must willingly give written informed consent prior to the start of the study.
- 5.1.7** All required imaging examination (CT, MRI, Bone Scintigraphy, MIBG Scintigraphy, and Gallium Scintigraphy) must be performed within 14 calendar days of each other and within 2 months of any diagnostic or operative procedure. Prior to treatment, whole-body MRI and PET (if PET is being done) must be performed, as well as at least one nuclear medicine test. In addition, a chest CT must be performed prior to treatment, except for those participants with neuroblastoma. In

participants with neuroblastoma, CT or MR of the primary must be performed prior to treatment. Chest CT is optional for those participants. Bone scintigraphy or MIBG scintigraphy will be acquired in participants with neuroblastoma. Bone scintigraphy will be performed in participants with rhabdomyosarcoma and other sarcomas. Gallium scintigraphy may be acquired in participants with lymphoma, but it is not required if PET is performed.

5.2 Exclusion Criteria For All Patients

- 5.2.1** Patient has contraindications for MRI or CT. This includes patients with active cardiac pacemakers or intracranial vascular clips.
- 5.2.2** Lack of parental permission (if participant is younger than 18) or lack of informed consent (if participant is 18 or older).
- 5.2.3** Patient has had a previous malignancy.
- 5.2.4** Patient has a CNS primary tumor.
- 5.2.5** Patient has osteosarcoma.
- 5.2.6** Pregnancy or nursing.

6.0 SITE SELECTION

6.1 Institution Requirements

- 6.1.1** Centrally reviewed studies will be filed at ACRIN headquarters. The protocol Quality Control Committee will be responsible for assuring that participating institutions have followed the protocols agreed to by the ACRIN investigators.
- 6.1.2** All institutions must have an approved General Qualifying Application (GQA) and an approved Protocol-Specific Application (both available on the web at www.acrin.org) on file at ACRIN headquarters in order to participate. See Appendix VI for details about additional site qualification requirements.

6.2 IRB Approval and Informed Consent

All institutions must have study-specific Institutional Review Board (IRB) approval. Research assistants must follow OHRP-approved consent procedures, as well as those set by the IRB at the institution. A copy of IRB approval and the sample IRB approved study-specific consent form must be on file at ACRIN Headquarters (fax 215-717-0936) prior to registering a participant.

6.3 Accrual Goals

Participants will be enrolled until 32 eligible participants with confirmed distant metastases who are evaluable for the primary endpoint have been accrued. We are 90% certain that the total sample size will be at most 226 participants. We expect that, among all participants accrued during a 3-month ramp-up and subsequent 12-month study accrual period, 20% will have neuroblastoma, 24% will have rhabdomyosarcoma, 12% will have other sarcomas, and 44% will have

lymphoma. Overall, 20% of participants are expected to present with distant metastases.

The ACRIN Biostatistics and Data Management Center will review accrual monthly, with the intention of discovering and resolving any problems. The ACRIN Steering Committee will be notified if total accrual is less than the number specified in the table below; at their discretion, they may re-evaluate the study with respect to feasibility. Particular attention will be paid to accrual 4, 8, and 12 months after the end of the 3-month ramp-up.

Months since end of ramp-up	Required cumulative accrual
1	15
2	29
3	43
4	57
5	71
6	85
7	100
8	114
9	128
10	142
11	156
12	170

The ACRIN Biostatistics and Data Management Center will also monitor the proportion of participants presenting with distant metastases. Once 100 participants with known truth status as determined by the accruing institution have been registered into the trial, the ACRIN Biostatistics Center will identify the proportion of them that presented with distant metastases, and re-estimate the 90th percentile for total sample size. The ACRIN Steering Committee will be notified of these results and, at their discretion, will then re-evaluate the study with respect to feasibility.

7.0 ONLINE REGISTRATION SYSTEM

7.1 Using the Online Registration System

Once the investigator-designated research staff (i.e. the Research Associate [RA]) has completed the eligibility checklist (Appendix II) and the participant has been found to be eligible, the participant may be consented. Upon obtaining a signed informed consent form, the information of the study participant will be registered by logging onto the ACRIN web site (www.acrin.org), which is available 24 hours a day, 7 days a week. Please refer to the **ACRIN Procedure Manual**, Section 7.1, **Participant Registration** for instructions.

7.2 Unsuccessful Registrations

7.2.1 ACRIN and protocol-specific requirements for institution participation are maintained within the administrative database. The protocol specific attributes are then interfaced with the web application for on-line

verification of site participation acceptance. If the institution has not met all the regulatory requirements based on the required attributions within the database, a screen that includes a brief explanation of the failure to gain access to the registration screens is projected. If during the completion of the eligibility questions a participant is deemed ineligible based on a response, a message box appears to instruct the research staff to contact the Data Management Center.

- 7.2.2** In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the DMC at the ACR (215-717-0936, ATTN: PARTICIPANT REGISTRATION). ACR staff will fax a response to the registering site with the confirmation of registration and participant case number as soon as possible.

8.0 DATA COLLECTION AND MANAGEMENT

8.1 General

- 8.1.1** The ACRIN web address is www.acrin.org.
- 8.1.2** Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at the ACRIN Data Management Department in Philadelphia.
- 8.1.3** Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the Data Management Center before attempting a re-registration.

8.2 Clinical Data Submission

- 8.2.1** Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars

will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN website. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

- 8.2.2** The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or until the study is terminated. The case is closed when all data have been received, reviewed and no outstanding data query exists for the case.
- 8.2.3** To submit data via the ACRIN website, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for missing data, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the "Complete Form Submission" button is depressed.
- 8.2.4** Once data entry of a form is complete, and the summary form reviewed for completeness and accuracy, the investigator or the research staff presses the "Complete Form Submission" button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data completed and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the Data Management Center for resolution of the submission.
- 8.2.5** If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the

DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

8.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

8.4 Electronic Data Management

8.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complimentary validation programs are initiated at the Brown Biostatistics Center and the Data Management Center. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC research associate. The validation program generated by BC produces a log of errors, which is sent to the DMC Research Associate (RA) for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC RA at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution. All BDMC communication with the participating sites is normally done through the Data Management Center.

8.4.2 If checks at DMC or BC detect missing or problematic data, the DMC RA sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC RA updates the participant's data submission calendar with the due date for the site RA or investigator's response.

8.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit

overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

8.6 Quality Assurance

8.6.1 The Biostatistical Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the Data Management Center (DMC). The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

8.6.2 A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the Biostatistical and Data Management Center (BDMC) will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance Department, until the problem has been resolved. If the BDMC, along with the Audit Group, cannot find a resolution to the problem, it will be brought to the Steering Committee for further discussion and resolution.

8.6.3 The BC, in conjunction with the DMC, will prepare frequent summaries of the accrued data to be presented to investigators. These summaries will report accrual rates (overall and by sub-groups of interest to the investigators), assess the completeness and accuracy of the data, and discuss any trends that may impact the outcomes of the trial. These intermittent summaries will not include analyses of the study's endpoints. Only planned interim analyses will be performed.

8.6.4 Image Quality Review

A review of a sampling of imaging procedures will be performed in order to ascertain the quality of image processing at the contributing institutions and to assure that the test is based on image processing of adequate quality. Copies of all imaging modalities used, including MRI and PET images from the first three cases from each institution, will be sent to the ACRIN image archive in Philadelphia. The image tests will be reviewed by the protocol Quality Control Committee at the ACRIN Image Laboratory in Philadelphia, or they will be sent to the protocol Quality Control Committee via the internet or on media for quality review. After

that time, a random sample of all MRI tests and PET scans and standard imaging tests will be reviewed for quality control purposes by a radiologist and a nuclear medicine physician.

8.6.5 In cases of suboptimal quality ratings, the study in question will be reviewed by the study PI and a decision will be made regarding eligibility for the study.

8.7 Records To Be Kept

The principal clinical investigator will maintain a file, separate from the clinic or hospital chart, which will contain the original consent form, eligibility checklist, and imaging evaluation forms.

9.0 DATA COLLECTION FORMS

9.1 Data Collection Forms

Form	Completed By
AO - Registration Form/Eligibility Checklist (Appendix II)	Clinical site
I1 - Initial Evaluation Form	Clinical site
C2 - CT Conventional Imaging Form	Clinical site
M4 - MRI Conventional Imaging Form	Clinical site
I6 - Scintigraphy Imaging Form	Clinical site
M3 - Whole-Body MRI Imaging Form	Clinical site
BX - Biopsy Form	Clinical site
IM - Proof of Truth in Diagnosis Form IE - Proof of Truth, 3 mos. IF - Proof of Truth, 6 mos.	Clinical site
O1 - Oncology Disease Staging Form	Clinical Site
CX - CT Reader Form	Central reader
MX - MRI Reader Form	Central reader
RS - Scintigraphy Reader Form	Central reader
QA - Whole Body MRI Data Quality Assessment Form	Quality Control Reader
QC - CT, MRI, Scintigraphy Data Quality Assessment Form	Quality Control Reader
DR - Diagnostic Imaging / Procedure Form	Clinical site
AE - Adverse Event Form	Clinical site
PR - Protocol Variation Form	Clinical site
I2 - CT Conventional Imaging	Images sent to ACRIN
I7 - MRI Conventional Imaging	Images sent to ACRIN
I3 - Whole-Body MRI Imaging	Images sent to ACRIN
I5 - Scintigraphy Imaging	Images sent to ACRIN
I4 - PET Imaging*	Images sent to ACRIN
TA - PET Technical Assessment Form*	Clinical site
PT - PET Form*	Clinical site
PX - PET Reader Form*	Central reader
F1 - Long Term Follow-up Form @ 1, 2, 3 Years	Clinical Site

* Only if optional PET is performed.

All imaging forms at local sites will be the same as central rereading forms and will be submitted to ACR as well.

9.2 Data Collection Table

	Form	Data Collection
A0	Registration	At time of registration via the ACRIN web site. Consists of Eligibility Checklist (Appendix II) and Participant Information.
I1	Initial Evaluation Form	Participant clinical history, submitted within 7 days of study registration.
C2	CT Conventional Imaging Form	Submitted within 21 days of imaging. Local reader. *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures (see Section 5.1).
M4	MRI Conventional Abd/Pelvis Imaging Form	Submitted within 21 days of imaging. Local reader. *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures (see Section 5.1).
I6	Scintigraphy Imaging Form	Submitted within 21 days of imaging. Local reader. *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures (see Section 5.1).
M3	Whole-Body MRI Imaging Form	Submitted within 21 days of imaging. Local reader. *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures (see Section 5.1).
BX	Biopsy Form	Submitted within 21 days of biopsy procedure. *Biopsy procedures: report one biopsy location per form.
IM	Proof of Truth in Diagnosis Form	Submitted at the end of clinical staging, repeated at 3 and 6 months from study enrollment. Any new procedures conducted after 6 months of enrollment and up to 36 months need to be submitted within 30 days of the procedure.
IE	Proof of Truth - 3 mos.	
IF	Proof of Truth- 6 mos.	
O1	Oncology Disease Staging Form	Submitted within 28 days of imaging
CX	CT Reader Form	Central read at ACRIN HQ.
MX	MRI Reader Form	Central read at ACRIN HQ.
RS	Scintigraphy Reader Form	Central read at ACRIN HQ.
QA	Whole Body MRI Data Quality Assessment Form	Completed by Quality Control Reader.

QC	CT, MRI, Scintigraphy Data Quality Assessment Form	Completed by Quality Control Reader.
DR	Diagnostic Imaging/Procedure Form	Submitted within 21 days of study registration.
AE	Adverse Event Form	Submitted within 30 days of first knowledge of event(s).
PR	Protocol Variation Form	Submitted in the instance a protocol requirement is not met; all information is necessary. Use a separate form for each case/instance.
I2	CT Conventional Imaging	Submitted within 21 days of imaging.
I7	MRI Conventional Imaging	Submitted within 21 days of imaging
I3	Whole-Body MRI Imaging	Submitted within 21 days of imaging.
I5	Scintigraphy Imaging	Submitted within 21 days of imaging.
I4	PET Imaging	Submitted within 21 days of imaging (if optional PET is performed).
TA	PET Technical Assessment Form	Optional Research Imaging Submitted within 21 days of imaging (if optional PET is performed).
PT	PET Form	Submitted within 21 days of imaging (if optional PET is performed). Local reader. *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures (see Section 5.1).
PX	PET Reader Form*	Optional Imaging – Central read at ACRIN HQ.
F1 –	F1 – Long Term Follow-up Form @ 1, 2, 3 Years	Submitted within 21 days of follow-up at years 1, 2, and 3 from study enrollment per form instructions.

*Only if optional PET is performed

10.0 IMAGE SUBMISSION

10.1 Digitally generated and scanned film diagnostic images can be transmitted to the ACRIN Image Management Center (IMC) via FTP directly to the image archive. The FTP site is located at <ftp://xray.acrin.org> or <ftp://206.137.103.34>. For each transmission a new folder for your institution and sub-folders for each corresponding exam must be created. Images are then to be transferred into those folders. An e-mail verifying the transfer and its contents including the name and number of exams as well as image count for each should be sent to both rwelsh@phila.acr.org and alevering@phila.acr.org. Please verify the transmission by examining the folders to make certain that all the images were received.

10.1.1 Please note that the header record on DICOM formatted image data, which often contains information identifying the participant by name, **MUST** be scrubbed before the image is transferred. This involves replacing the Participant Name tag with the Institution ID or number, replacing Participant ID tag with the ACRIN case number, and putting the study number into the Other Participant ID tag. This

can either be done by software present at the institution or software available from the ACRIN DMC.

- 10.1.2** In the event that either DICOM capability or transfer of scrubbed image headers is not available, images may also be sent on a CD or other electronic medium for the ACRIN IMC to transfer to the image archive. Please contact the ACRIN IMC prior to sending the media to confirm compatibility.
- 10.1.3** Where applicable, images from outside institutions should be sent to the ACRIN IMC via CD or ACRIN electronic transfer (see Section 10.1).
- 10.1.4** Images stored on the ACRIN IMC image archive will then be routed to other sites involved using either FTP or CD-ROM where appropriate for purposes of secondary interpretation.

11.0 IMAGING ASSESSMENT

Details of the CT, MRI, Bone Scintigraphy, and PET techniques are available on the ACRIN web site at (http://www.acrin.org/6660_protocol.html). For more detailed information, contact Anthony Levering (alevering@phila.acr.org).

11.1 Rhabdomyosarcoma and Other Sarcomas

11.1.1 Order and Timing of Studies

Imaging tests to be obtained at presentation include chest CT, abdominal/pelvic CT, bone scintigraphy, or conventional MRI as indicated and whole-body MRI and, optionally, FDG-PET. All required imaging tests (CT, MRI, and scintigraphy) for staging must be performed within 14 calendar days of each other and within 2 months of any diagnostic or operative procedure. Prior to treatment, whole-body MRI and PET (if PET is being done) must be performed, as well as at least one nuclear medicine test. In addition, a chest CT must be performed prior to treatment.

11.1.2 Computed Tomography and/or Conventional MRI

All participants will undergo pre-treatment chest CT scans as a screen for pulmonary metastases. This is routine standard care for participants with solid soft-tissue masses. Participants may also undergo abdominal CT or conventional MRI as a screen for occult hepatic and nodal metastases. Where clinically indicated, participants will have a head CT or MRI to rule out metastatic disease.

11.1.3 Bone Scintigraphy

Skeletal scintigraphy is a routine staging test for virtually all participants with small round blue cell tumors to screen for skeletal metastases and will be acquired in this study routinely.

11.1.4 Plain Films

For single lesions detected on bone scintigraphy, radiographs of the abnormal areas will be done in a minimum of 2 views.

11.1.5 Whole-Body MRI

Whole-body MRI techniques will be used as the index test, or experimental part of this protocol in participants with small cell neoplasms. The study will include the entire body from the vertex of the skull to the upper extremities, including wrists to lower extremities, including ankles, which are potential sites of red marrow in children and, thus, potential sites for metastases. Two different MRI techniques will be used to screen for metastases. Three to four sets of coronal images will be obtained, depending on the size and age of the participant.

11.1.6 FDG-PET

FDG-PET is an optional index test in this study. The extent of the PET scan will vary with participant age and site of tumor. For young participants under age 5 years, the study will include the entire body from the vertex of the skull to the upper extremities, including wrists to lower extremities, including ankles. In older children, the study will extend from the base of the skull to the lower femurs. The scan extent will be limited in older children to limit the imaging time. In addition, in older children the sites of metastases are more likely to be limited to the red marrow in the spine, ribs, pelvis, proximal humeri, and femora.

11.2 Neuroblastoma

11.2.1 Order and Timing of Studies

Imaging tests to be obtained at presentation include CT or conventional MRI, bone scintigraphy, and whole-body MRI and, optionally, FDG-PET and MIBG. If MIBG is performed, bone scintigraphy must be obtained. All required imaging tests (CT, MRI, and scintigraphy) for staging must be performed within 14 calendar days of each other and within 2 months of any diagnostic or operative procedure. Prior to treatment, whole-body MRI and PET (if PET is being done) must be performed, as well as at least one nuclear medicine test. In addition, a chest CT must be performed prior to treatment, except for those participants with neuroblastoma. In participants with neuroblastoma, CT or MR of the primary must be performed prior to treatment. Chest CT is optional for those participants.

11.2.2 Computed Tomography and/or Conventional MRI

All participants will undergo pre-treatment chest or abdominopelvic CT scans or conventional MRI, depending on the site of the primary tumor. This is standard care for patients with neuroblastoma to evaluate the extent of the primary tumor. Participants with primary abdominopelvic tumors may also undergo chest CT as a screen for occult pulmonary metastases. Where clinically indicated, participants will have a head CT or brain MRI to rule out metastatic disease.

11.2.3 Bone Scintigraphy

Skeletal scintigraphy and/or MIBG scintigraphy are routine staging tests for virtually all participants with neuroblastomas to screen for skeletal metastases and either test will be acquired in this study routinely.

11.2.4 Plain Films

For single skeletal lesions detected on bone scintigraphy, radiographs of the abnormal areas will be done in a minimum of 2 views.

11.2.5 Whole-Body MRI

Whole-body MRI techniques will be used as the index test, or experimental part of this protocol, in participants with neuroblastomas. The study will include the entire body from the vertex of the skull to the upper extremities, including wrists to lower extremities, including ankles, which are potential sites of red marrow in children and thus sites for metastases. Two different MRI techniques will be used to screen for metastases. Three to four sets of coronal images will be obtained, depending on the size and age of the participant.

11.2.6 FDG-PET

FDG-PET is an optional index test in this study. The extent of the PET scan will vary with participant age and site of tumor. For young participants under age 5 years, the study will include the entire body from the vertex of the skull to the upper extremities, including wrists to lower extremities, including ankles. In older children, the study will extend from the base of the skull to the lower femurs. The scan extent will be limited in older children to limit the imaging time. In addition, in older children the sites of metastases are more likely to be limited to the red marrow in the spine, ribs, pelvis, proximal humeri, and femora.

11.3 Lymphoma

11.3.1 Order and Timing of Studies

Imaging tests to be obtained at presentation include chest and abdominal CT scans, whole-body MRI, and either FDG-PET or gallium scintigraphy. All required imaging tests (CT, MRI, and scintigraphy, if scintigraphy is being done) for staging must be performed within 14 calendar days of each other and within 2 months of any diagnostic or operative procedure. Prior to treatment, whole-body MRI and PET (if PET is being done) must be performed, as well as at least one nuclear medicine test. In addition, a chest CT must be performed prior to treatment.

11.3.2 Computed Tomography and/or Conventional MRI

All participants will undergo pre-treatment chest or abdominopelvic CT scans. This is standard care for patients with lymphoma to evaluate the extent of the primary tumor. Where clinically indicated, participants will have a head CT or brain MRI to rule out metastatic disease.

11.3.3 Gallium Scintigraphy

Gallium scintigraphy is an accepted test to stage participants with lymphoma, but in many institutions has been supplanted by FDG-PET. Gallium scintigraphy will be acquired in this study if FDG-PET is not performed.

11.3.4 Plain Films

For single lesions detected on gallium scintigraphy or FDG-PET, radiographs of the abnormal areas can be obtained.

11.3.5 Whole-Body MRI

Whole-body MRI techniques will be used as the index test, or experimental part of this protocol, in participants with neuroblastomas. The study will include the entire body from the vertex of the skull to the upper extremities, including wrists

to lower extremities, including ankles, which are potential sites for metastases. Two different MRI techniques will be used to screen for metastases. Three to four sets of coronal images will be obtained, depending on the size and age of the participant.

11.3.6 FDG-PET

FDG-PET is an optional index test in this study. The extent of the PET scan will vary with participant age and site of tumor. For participants under age 5 years, the study will include the entire body from the vertex of the skull to the upper extremities, including wrists to lower extremities, including ankles. In older children, the study will extend from the base of the skull to the lower femurs. The scan extent will be limited in older children to limit the imaging time. In addition, in older children the sites of metastases are more likely to be limited to the red marrow in the spine, ribs, pelvis, proximal humeri, and femora.

12.0 IMAGE INTERPRETATION

12.1 Local Image Interpretation

Imaging tests will be interpreted following the practice of each site. Information may be used for treatment planning, as determined on an individual basis by each site.

12.2 Central Image Interpretation (Reader Studies)

12.2.1 A reference set showing examples of interpretation data will be used to standardize interpretation quality of study radiologists.

12.2.2 All imaging tests will be assessed for distant tumor extent, including metastases to lung, brain, liver, bone, bone marrow, and non-regional lymph nodes.

12.2.3 The study sample for central image interpretation will be composed of 32 participants with, and 32 participants without, Stage IV disease, as determined by the truth panel (see Section 15.0). Participants will be randomly selected from within these groups. The sample will then be divided into two reading groups of 32 participants each. Each set will contain some participants with, and some participants without, Stage IV disease.

The readers for central image interpretation will be 10 study pediatric radiologists and 10 nuclear medicine specialists, formed into reading pairs (to mimic clinical practice).

12.2.4 Central image interpretation for each reader pair will occur over two sessions sufficiently separated in time to minimize any potential for recall bias. In each session, each reader pair will interpret index tests (whole-body MRI and optional FDG-PET) for one reading group, and conventional imaging tests (CT/conventional MRI for distant staging and bone scans) for another reading group. To accommodate schedules, sessions for all reader pairs will likely not be concurrent.

Interpretations will first be made independently of each other, and without knowledge of the results of other tests or of the reference standard. The pediatric

radiologist will interpret whole-body MRI, CT, and conventional MRI images. For whole-body MRI, the turbo STIR images will be read first without and then, in the same session, with OOPS images; the final interpretation will be used for evaluating accuracy of whole-body MRI. The nuclear medicine specialist will interpret the bone scans and any optional PET studies. After their independent interpretations, a second paired reading of conventional imaging tests (i.e., excluding whole-body MRI) will be done, and this joint interpretation will be used to determine the accuracy of conventional imaging.

Readings	Session 1	Session 2
Radiologist alone, Nuclear medicine specialist alone, then Reader pair	Subset 1: Experimental	Subset 2: Experimental
	Subset 2: Conventional	Subset1: Conventional

12.2.5 Whole-body MRI and Optional FDG-PET

Study radiologists will interpret whole-body MRI examinations without knowledge of conventional imaging tests or optional FDG-PET imaging. Study nuclear medicine specialists will interpret PET imaging examinations without knowledge of conventional imaging tests or whole-body MRI. Later in the same session, each radiologist-nuclear physician pair (see Section 12.2.4) will perform a joint interpretation of the whole-body MRI (including turbo STIR and out-of-phase imaging) and PET imaging examinations for all participants having undergone PET imaging, still without knowledge of conventional imaging tests.

12.2.6 Guidelines for Analysis

- 12.2.6.1** The diagnosis of bone/bone marrow metastases on MRI will be based on the following: areas of diffuse or focal high-signal-intensity changes in cortical bone or bone marrow on either whole-body MRI sequence.
- 12.2.6.2** The diagnosis of bone marrow metastases on scintigraphy (bone, MIBG, or gallium) and on FDG-PET images will be based on one or more focal areas of increased activity on the images. The diagnosis of bone/bone marrow metastases on PET will be based on the identification of abnormal uptake as being greater than normal activity on the attenuation-corrected images.
- 12.2.6.3** Lung metastases are defined as foci of soft tissue attenuation on CT or high signal intensity on MRI. Liver metastases are defined as foci of abnormal low attenuation on CT or high signal intensity on MRI. Diagnosis of lung metastases on PET will involve the identification of abnormal uptake as being greater than normal activity on the attenuation-corrected images.
- 12.2.6.4** In children under 10 years of age, any visualized intrathoracic or intraabdominal lymph node will be considered abnormal, regardless of size. In older children, a lymph node will be considered abnormal on CT, conventional MRI, or whole-body MRI if the largest transverse diameter exceeds 1 cm. The diagnosis of lymph node infiltration by

tumor on PET will involve the identification of abnormal uptake as being greater than normal activity on the attenuation-corrected images.

13.0 CONFIRMATORY STUDIES FOR POSITIVE FINDINGS ON WHOLE-BODY MRI AND FDG-PET

13.1 Whole-Body MRI or PET Positive Liver Lesions

If a liver abnormality is recorded, a detailed hepatic CT, MRI or sonogram may be used to confirm metastatic disease. These imaging tests may be used without biopsy to diagnose hemangiomas or benign cysts. If these tests show a solid lesion, biopsy will be suggested. However, it is sometimes not practical to biopsy very small lesions. In addition, biopsies in small children who require sedation may not be practical.

13.2 Whole-Body MRI or PET Positive Bone Lesions

Osseous or marrow abnormalities seen on any imaging test may be further evaluated by appropriate imaging tests (plain radiographs, CT, dedicated MRI, or bone scintigraphy in participants who did not undergo these examination initially, if considered clinically appropriate), or by biopsy, or by both in order to confirm metastatic disease.

13.3 Whole-body MRI or PET Positive Brain Lesions

An abnormality of the brain may be assessed by CT or MRI with contrast enhancement.

13.4 Whole-body MRI or PET Positive Lung Lesions

An abnormality of the lung not seen on any other imaging test may be assessed by a thinly collimated chest CT scan.

13.5 Lesions Not Biopsied

A lesion reported as a probable metastasis on any imaging test but not biopsied will be considered a false-positive imaging result if it remains unchanged over a six-month follow-up. If a lesion appears on imaging tests but is not able to be biopsied, repeat imaging is requested at 3 to 6 months for follow-up. In participants who have a lesion (or lesions) detected on imaging tests but not confirmed by biopsy, repeat standard imaging is recommended at 3 to 6 months for follow-up.

13.6 Treatment for Participants With Suspected Metastases

When any imaging test identifies an abnormality that is considered highly suspicious for a metastasis, or when biopsy proof of that metastasis is obtained, the participant receives treatment at the discretion of the treating physician.

14.0 FOLLOW UP

In participants who have a lesion (or lesions) detected on whole-body MRI or PET at initial staging that are not confirmed by biopsy or other conventional imaging tests at

staging, repeat standard imaging is recommended at 3 to 6 months for follow-up at the discretion of the treating physician.

When whole-body MRI or FDG-PET identifies an abnormality, which is considered highly suspicious for a metastasis, or when biopsy proof of that metastasis is obtained, the participant receives treatment at the discretion of the treating physician.

Long-term clinical follow-up may be obtained from the treating physician at years 1, 2, and 3 from study enrollment to examine event-free survival, the impact of the research imaging on participant staging and treatment, and the relationship of the research imaging to relapse.

15.0 PROOF OF TRUTH IN DIAGNOSIS

A panel of experts including a pediatric oncologist (“truth panel”) will review all available clinical history and initial, 3-month and/or 6-month follow-up diagnostic tests (e.g., CT, conventional MRI, bone, MIBG or gallium-scintigraphy, bone marrow aspiration or biopsy, surgical biopsy of bone skeletal or visceral lesions, operative report), excluding the whole-body MRI or FDG-PET studies to determine the reference standard of an overall diagnosis (metastatic tumor vs. no metastatic tumor). The truth panel will use their best clinical judgment and all available information through 6 months of follow-up to arrive at a conclusion about the reference standard.

Histologic confirmation is most likely to be obtained if there is a solitary lesion. However, it is expected that most metastases will not be biopsied and the diagnosis will be made on one or more non-invasive imaging tests.

16.0 ADVERSE EVENT REPORTING

16.1 Definition of Adverse Event

An Adverse Event (AE) is any untoward, undesired, unplanned medical occurrence in a participant, and does not necessarily have a causal relationship with the study intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study, including intercurrent illnesses or injuries, should be regarded as an adverse event.

16.2 Definition of Serious Adverse Event

Adverse events are classified as serious or non-serious. A Serious Adverse Event (SAE) is any adverse event that results in any of the following outcomes:

- Death;
- Life-threatening (refers to any adverse event that places the subject at immediate risk of death from the event as it occurred; life-threatening event does not include

- an event that, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death);
- Inpatient hospitalization and/or prolongation of an existing hospitalization (hospitalization refers to an overnight admission). Emergency room visits are not considered serious until one of the above criteria is met. Any elective hospitalization for a pre-existing condition that has not worsened does not constitute a serious adverse event;
 - Results in persistent or significant disability or incapacity (substantial disruption in a person's ability to conduct normal daily living activities);
 - A congenital anomaly or birth defect (in offspring); or
 - Other medically important event.

Important medical events are those based upon appropriate medical judgment that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

If there is any doubt whether the adverse event constitutes a serious adverse event, it should be considered and treated as serious and reported to appropriate ACRIN personnel at 215-574-3150.

16.3 Adverse Event Grading

Grade refers to the severity (intensity) of the adverse event.

- 1 – **Mild:** AE is noticeable to the participant but does not interfere with routine activity.
- 2 – **Moderate:** AE interferes with routine activity but responds to symptomatic therapy and/or rest
- 3 – **Severe:** AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy
- 4 – **Life-threatening or disabling**
- 5 – **Death/Fatal**

16.4 Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a study treatment or procedure. An adverse event may be considered **associated** with the study treatment or procedure if there is a reasonable possibility that the adverse event was caused by the whole body MRI. An adverse event may be considered **NOT associated** with the study treatment/procedure if there is not a reasonable possibility that the adverse event was caused by the whole body MRI.

Attribution categories are:

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

16.5 Expected Adverse Events

Whole-Body MRI:

- Anxiety/Stress
- Claustrophobia
- Discomfort
- False positive study-related imaging findings that result in unnecessary biopsies will be considered an adverse event and will be reported on the Adverse Event Case Report Form (AE CRF).

Sedation, if prescribed and accepted:

- Allergic reaction to anesthesia
- Adverse interaction with other medications
- Suppression of airway reflexes
- Respiratory depression/arrest
- Cardiovascular decompensation
- Reduction of gross motor skills
- Death

16.6 Recording of Adverse Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on adverse events through discussion and, as appropriate, by examination. Information on all expected and unexpected adverse events considered possibly, probably, definitely related to the whole-body MRI trial with the severity level of grades 1, 2, 3, 4, 5 should be recorded immediately into the source document, e.g. adverse event log and/or progress notes of the study participant's chart, and retained at the site. These adverse events will also be recorded in the AE CRF and reviewed by the principle site investigator in real time to determine grade and attribution of the event.

A **pre-existing condition** is one that is present at the start of the study. A pre-existing medical condition is defined as an adverse event if the frequency, intensity, or character of the medical condition worsens during the study period. At screening visit, any clinically significant findings/abnormalities should be recorded as a pre-existing condition. At the end of study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be documented as adverse events.

16.7 Reporting of Adverse Events

Prompt reporting of all adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research.

Routine reporting is defined as documentation of adverse events on source documents and AE CRF, and submission to ACRIN for preparation of a report for Data and Safety Monitoring Committee (DSMC) review, quarterly reports to CDUS, and the final study report.

Expedited reporting is defined as immediate notification of NCI and ACRIN per section 16.8. Routine reporting requirements also apply.

Since this is a diagnostic study that does not involve any experimental forms of cancer therapy, adverse event reporting will be minimal. ACRIN will collect and report only those adverse events considered possibly, probably, or definitely related to the whole body MRI trial that occur during study participation and up to 30 days after the last study procedure. Local IRBs and/or institutions may stipulate additional adverse events reporting based upon their review of the protocol.

All expected and unexpected adverse events considered possibly, probably, or definitely related to whole-body MRI and serious adverse events identified in section 16.8 will be documented in the study participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, NCI/CIP, and the local IRB (per local IRB policy).

16.8 Expedited Reporting To NCI and ACRIN

16.8.1 Investigator or investigator-designee must use expedited adverse event reporting for **all deaths** occurring during study participation and up to 30 days after the last study procedure, regardless of attribution and regardless of whether the event was expected or unexpected.

16.8.2 All life-threatening/disabling unexpected adverse events (considered possibly, probably, or definitely related to the whole body MRI trial) occurring during study participation and up to 30 days after the last study procedure will be reported within ten (10) working days of first knowledge of the event. These reports should be sent to ACRIN, NCI's Cancer Imaging Program (CIP), and the local Institutional Review Board (IRB), in addition to documentation in patient chart and AE CRF.

16.8.3 All hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAEv3.0 Grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the whole body MRI trial must be reported within ten (10) working days of first knowledge of the event, in addition to documentation in patient chart and AE CRF.

16.8.4 All other serious adverse events with attribution of possibly, probably, or definitely related to the whole body MRI trial which include AEs that result in persistent or significant disability or incapacity, or congenital anomaly (birth defect) in the offspring of the study participant must be reported within ten (10) working days of first knowledge of the event during study participation and up to 30 days after the last study procedure, in addition to documentation in patient chart and AE CRF.

16.8.5 Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on on-going serious adverse events should be promptly reported to ACRIN.

16.9 How to Report

16.9.1 All serious adverse events and adverse events meeting the requirement for expedited reporting: an expedited adverse event report requires submission to the NCI-CIP and ACRIN using the paper templates “Adverse Event Expedited Report (AdEERS)—Single Agent” available on the CTEP home page, <http://ctep.info.nih.gov>.

16.9.2 Protocols involving imaging procedures must be submitted using a paper version. Omit the Course Information section and the Protocol Agent section, even though the template indicates those sections as mandatory.

Do not try to send the form via the web site; it will not accept a form without those fields filled in.

16.9.3 Completed expedited reports should be sent to:

Barbara Galen, MSN, CRNP, CNMT, Program Director
Re: Adverse Event Report
Cancer Imaging Program
6130 Executive Blvd., MSC 7412,
Room 6050
Bethesda, MD 20892-7412

To make a telephone report, contact NCI at (301) 496-9531, available 24 hours a day (recorder available after hours from 5 PM to 9 AM Eastern Time). A copy of all expedited adverse event reports should be sent to NCI by fax at (301) 480-3507, followed by a hard copy via US Mail.

16.9.4 A copy of all expedited adverse event reports should be sent to ACRIN by fax at (215) 717-0936. All fatal adverse events should be reported by telephone within 24 hours of the first knowledge of the event. To make a telephone report to ACRIN, call (215) 717-2763, available 24 hours a day (recorder after hours from 5 PM to 8 AM Eastern Time).

16.9.5 All expedited adverse event reports should be sent to your local Institutional Review Board (IRB). Adverse events not requiring expedited reporting are normally reported to your local IRB in an annual report and/or continuing review. Please refer to your local institution’s IRB policies regarding adverse events and serious adverse events and safety reports.

17.0 STATISTICAL CONSIDERATIONS

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18.0 ETHICAL CONSIDERATIONS

18.1 Institutional Review Board Approval

It is the site investigator's responsibility to ensure that this protocol is reviewed and approved by the appropriate Institutional Review Board (IRB). Each clinical site must obtain a letter of approval from the IRB (full board review) prior to registering participants. The IRB must also review and approve the site's informed consent document and any other written information provided to the participant prior to any registration of participants.

A copy of IRB approval letter for the protocol and sample of IRB approved informed consent document must be submitted to ACRIN (fax 215-717-0936).

If, during the study, it is necessary to amend either the protocol or informed consent document, the investigator will be responsible for ensuring the IRB reviews and approves the amended documents. IRB approval of the amended informed consent document must be obtained before new patients consent to participate in the study using this version of the consent.

18.2 Informed Consent Process

The investigator or his/her designee will inform the participant, participant's parents or legally authorized representative of all aspects pertaining to the participant's participation in the study. The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The informed consent document must be signed and dated by the investigator (or his/her designee) and the participant's parents (or legally authorized representative) BEFORE the patient can participate in the study. The original dated document will be retained in the participant's study file or medical record and must be available for review at the time of an audit.

18.3 Protection of Participant Rights

18.3.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human subject research. This is accomplished through the IRB oversight. The IRB reviews all proposed studies involving human subject research and ensures that the participant's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the Informed Consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

18.3.2 Confidentiality of Participant Data

The clinical site is responsible for the confidentiality of the data associated with participants registered in this study in the same manner it is responsible for the confidentiality of any participant data within its sphere of responsibility. Federal regulations govern the protection of participants’ rights relative to data confidentiality and use of research data.

18.3.3 Inclusion of Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the projected gender and minority accruals are shown below:

Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	5	6	0	11
Not Hispanic or Latino	92	123	0	215
Unknown	0	0	0	0
Ethnic Category: Total of all subjects	97	129	0	226
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	2	3	0	5
Black or African American	23	29	0	52
Native Hawaiian or other Pacific Islander	0	0	0	0
White	70	95	0	165
More than one race	0	0	0	0
Unknown	2	2	0	4
Racial Category: Total of all subjects	97	129	0	226

The estimates were obtained based on data received from the Mallinckrodt Institute of Radiology, St. Jude Children’s Research Hospital, and Egleston Children’s Hospital. A minimum of 1 year’s worth of data was given from each institution, in which the gender, race, and ethnicity were reported for all patients who were seen at the institution with any of the tumors under consideration for this study. This information was then pooled to provide the overall study estimates. ACRIN is, however, an open network and therefore cannot determine a priori the gender and minority distributions across all institutions that may ultimately participate in the trial.

19.0 INSTITUTIONAL AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, and ACRIN. The

investigator will ensure the capability for inspection of all participating site's study-related facilities (e.g. imaging center, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits

Institutional on-site audits will be completed within 18 months of a site's enrolling its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit. Auditors will follow procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparing for the audit will be sent to sites in advance of the audit date. With these instructions, the auditors will specify which case records will be reviewed during the audit. Auditors will review on-site records against the reviewed data, and they will record their findings on specially prepared questionnaires. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will be also reviewed at the audit. In particular, the auditors will ensure that the correct version of the consent form (see Appendix I for all four versions of the study consent forms) was signed by each participant.

To help sites prepare for audits and assure that the investigator and the research staff maintains records appropriately, the ACRIN data management and auditing staff will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial. Please refer to Section 19.4, Audit Source Documentation Table, for details.

19.1 Source Documents

Source data are found in all information, original records of 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. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN.

Source documents must verify the eligibility criteria and data submitted on all case report forms (CRFs). If an item is not mentioned (e.g., history and physical with no mention of a psychological condition), it will be assumed it is not present.

Research records for each case should contain copies of the source documents for the data reported to ACRIN. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This will prevent any discrepancies and the inability to verify the document and the data reported.

19.2 Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case, "N/A" must be noted. All entries must be printed legibly in black or blue ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires may be documented on the CRF. The image interpretation data required by the study that is a more detailed extraction of information from the image and is not typically documented in the standard radiology report may be recorded on the CRF and is accepted as source documentation if signed by the Investigator. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant questionnaire, CT, MR, etc.).

Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a deficiency.

19.3 Institutional Review Board

Sites must obtain local IRB initial approval. Prior to subject registration, a copy of the IRB approval letter for the protocol and the informed consent form must be sent to ACRIN, along with a copy of IRB approved informed consent form. Investigator will provide copies of IRB approval letter(s) for any amendments, and copies of annual renewal(s).

19.4 Audit Source Documentation Table

Form	Data Collection	Source Documentation
A0 Registration (Appendix II) At time of registration via the ACRIN web site.	Consists of Eligibility Checklist (Appendix II) and Participant Information (participant hospital medical records, participant clinic chart, pathology reports, biopsy reports, imaging reports [CT, MR, Nuclear Medicine], etc. as defined in Protocol Section 5.0)	Participant Information and completed, signed (Research Associate) and dated AO form, after signed consent. Note: Participant/parent signature is required if the AO information has been obtained through participant/parent interview or self-completion of the form.
I1 Initial Evaluation Form Completed at the time of study registration.	Participant clinical history, submitted within 7 days of registration. Participant Information (participant hospital medical records, participant clinic chart, pathology reports, biopsy reports, imaging reports [CT, MR, Nuclear Medicine], etc. as defined in Protocol Section 5.0)	Participant Information and completed, signed (Research Associate) and dated I1 form. Note: Participant/parent signature is required if the I1 information has been obtained through participant/parent interview or self-completion of the form.
C2 CT Conventional Imaging Form	Submitted within 21 days of imaging. Local Reader *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures. Protocol - sec. 5.1.5	Completed, signed (Radiologist) and dated C2 form. AND CT Report
M4 MRI Conventional Abd/Pelvis Imaging Form	Submitted within 21 days of imaging. Local Reader *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures. Protocol - sec. 5.1.5	Completed, signed (Radiologist) and dated M4 form. AND MRI Report
I6 Scintigraphy Imaging Form	Submitted within 21 days of imaging. Local Reader *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures. Protocol - sec. 5.1.5	Completed, signed (Radiologist) and dated I6 form. AND Nuclear Medicine Report Note: Check for type of procedure (Question 6 on form).
M3 Whole-body MRI Imaging Form	Submitted within 21 days of imaging. Local Reader *All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures. Protocol - sec. 5.1.5	Completed, signed (Radiologist) and dated M3 form. AND Whole-body MRI Report

PT	PET Form	<p>Optional Imaging.</p> <p>Submitted within 21 days of imaging. Local Reader</p> <p>*All imaging to be done within 14 calendar days of each other and within 2 months of diagnostic/operative procedures. Protocol - sec. 5.1.5</p>	<p>Completed, signed (Radiologist) and dated PT form.</p> <p>AND PET Report</p>
BX	Biopsy Form	<p>Submitted within 21 days of Biopsy Procedure.</p>	<p>Completed and signed (Research Associate & Radiologist and/or Pathologist) and dated BX form.</p> <p>AND Reports: Diagnostic procedure report(s) and pathology report(s)</p> <p>Note: Biopsy procedures – report one biopsy location per form.</p>
IM IE IF IS	<p>“Proof of Truth” Diagnosis Form</p> <p>Additional Forms: “Proof of Truth” Diagnosis Forms</p>	<p>Submitted at the end of the <u>initial</u> clinical staging, includes details of initial Pathology. Submission dates: “window of completion” is plus or minus 3 weeks from the form due date.</p> <p>Additional Forms: IE - 3 month follow-up IF - 6 month follow-up IS - Any <u>new</u> surgery, diagnostic procedure, or imaging procedure occurring after 6 months of enrollment and up to 36 months.</p>	<p>Completed, signed (Site Oncologist & Research Associate) and dated IM form.</p> <p>Additional Forms: Completed, signed (Site Oncologist & Research Associate) and dated IE/IF/IS forms.</p>
O1	Oncology Disease Staging Form	<p>Submitted within 28 days of imaging.</p>	<p>Completed, signed (Site Oncologist), and dated O1 form.</p>
DR	Diagnostic Imaging/ Procedure Form	<p>Submitted within 21 days of study registration.</p>	<p>Completed, signed, (Research Associate) and dated DR form.</p> <p>AND Reports: All relative diagnostic imaging reports.</p>
AE	Adverse Event Form	<p>Submitted within 30 days of first knowledge of the event.</p>	<p>Completed, signed, (Site Principal Investigator) and dated AE form.</p> <p>AND Medical record/progress note documentation of the event.</p>
PR	Protocol Variation Form	<p>Submitted in the instance a protocol requirement is NOT met, all information is necessary.</p> <p>A separate form for <u>each</u> case/instance.</p>	<p>Completed, signed, (Research Associate) and dated PR form.</p>

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APPENDIX I: SAMPLE CONSENTS

ACRIN 6660: WHOLE-BODY MRI IN THE EVALUATION OF PEDIATRIC MALIGNANCIES

SAMPLE CONSENT FOR RESEARCH STUDY—Participants under 18 years of age

This is a clinical trial (a type of research study). Clinical trials include only participants who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need to Know,” is available from your doctor.

Your child is being asked to be in this study because he/she has a type of cancer that can spread to other areas of the body. Researchers are trying to find the best way to see if and where the cancer has spread (metastatic disease).

WHY IS THIS STUDY BEING DONE?

The standard tests that are used to determine the extent and spread of your child’s disease are magnetic resonance imaging (MRI), computed tomography (CT) and bone scanning, gallium scanning, metaiodobenzylguanidine (MIBG) scanning, and/or positron emission tomography (PET) scanning. The purpose of this study is to determine if a newer imaging test referred to as whole-body MRI can detect the extent and spread of disease as accurately as the standard tests. The results of whole-body MRI will be compared with those of conventional imaging (standard studies) for detecting distant metastases.

Whole-body MRI is a diagnostic test that uses a large magnet to take pictures of the body with rapid imaging times. Up to now it has not been used routinely in the evaluation of all children with cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 226 participants age 21 years and younger will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If your child takes part in this study, he/she will have the following tests and procedures:

- Conventional Imaging Tests: May include MRI, CT, Bone Scan, Gallium Scan, MIBG Scan, and/or PET scan.
- Experimental Imaging Test: Whole-Body MRI.

Standard needle or surgical biopsy and/or bone marrow aspiration or clinical follow-up will be done as standard care to confirm diagnosis of metastatic disease.

The experimental whole-body MRI studies are conducted in the same way as the routine MRI studies except the overall time your child will spend in the MRI unit is significantly shorter and no i.v. contrast is needed. The whole-body MRI will be performed at the time of initial diagnosis. For this test, your child will lie in a long tube of the magnetic resonance scanner on his or her back for about 15 to 30 minutes.

If your child is frightened or cannot lie still, he or she may need sedation. If you don't elect sedation, you may withdraw from this study.

HOW LONG WILL MY CHILD BE IN THE STUDY?

The length of time your child will be in the study will be six (6) months. During the follow-up time, your child will undergo imaging tests and biopsies for the management of their specific disease. After the initial research imaging is done, your child's doctor will continue to follow how your child is doing with his/her treatment and follow-up. Your child's information may be collected as part of clinical follow-up at years one (1), two (2), and three (3) from the time of your child's initial research imaging. Your child's doctor for the study will provide this information.

Your child can stop participating in this study at any time. However, if you decide to stop his/her participation in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While your child is on the study, he/she is at risk for the side effects listed below. You should discuss these with the researcher and/or your child's regular doctor.

The side effects associated with the experimental imaging test are the same as those associated with the standard tests used for diagnosis. Because whole-body MRI is an additional test, it increases the risk of false positive results, as any imaging test can; false positive results can cause anxiety or unnecessary biopsies.

Side Effects Associated with Whole-Body MRI

Likely:

The MRI scanner room is kept cool, and your child may experience some discomfort from being cold, but he or she will be given a blanket. The scanner makes a loud knocking noise when it is taking pictures, but your child will be given earplugs, or he or she may put on headphones and listen to the radio.

Less likely:

Your child may experience some claustrophobia or some anxiety about being in the long tube of the scanner. If your child needs to get out of the scanner at any time, the technologist can hear their request.

There is the risk of increased anxiety or stress associated with the whole-body MRI study demonstrating the possibility of tumor somewhere in your child's body. Some participants or parents may be anxious regarding this uncertainty of test results. In addition, there is the risk that whole-body MRI study findings will lead to a need for more testing (such as x-rays, nuclear medicine scans, or biopsy) and that your child will be found to have a more advanced stage of disease requiring more aggressive treatment.

Side Effects Associated with Sedation

Sedation may be needed in younger children for the whole-body MRI scans.

Rare:

Allergic reaction to the anesthesia, adverse interaction with other medications, suppression of airway reflexes, cardiovascular decompensation, reduction of gross motor skills, and death.

Reproductive Risks:

Participants in this study must not be pregnant or nursing. Talk with your child's physician about the risks associated with pregnancy during cancer treatment.

ARE THERE POTENTIAL BENEFITS TO TAKING PART IN THE STUDY?

If you agree for your child to take part in this study, there may or may not be direct medical benefit to him or her. We hope the information learned from this study will benefit other children who have a similar disease in the future. If the whole-body MRI studies prove to be as accurate as the standard diagnostic procedures it will make the evaluation of children with this, or a similar disease, simpler and faster than with the current tests. The whole-body MRI may improve the accuracy of assessing the extent of disease of your child's tumor.

WHAT OTHER OPTIONS ARE THERE?

If you choose not to participate in this study the care of your child will not be affected. All tests used in the study are available to patients without being registered on this protocol.

WHAT ABOUT CONFIDENTIALITY?

You understand that every attempt will be made by the investigators to keep all the information collected in this study strictly confidential, including your child's personal information. We cannot guarantee absolute confidentiality. Records of your child's progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN). All data sent to ACRIN over the Internet will be coded so that other people cannot read it. Your child's personal information may be disclosed if required by law.

You further understand that authorized representatives of ACRIN, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the local Institutional Review Board (IRB) and other groups or organizations that have a role in this study will have access to and may copy both your child's medical and research records due to your child's participation in this study. This access is necessary to ensure the accuracy of the findings and your child's safety and welfare. If any publication or presentations result from this study, your child will not be identified by name. Results will be reported in a summarized manner in which your child cannot be identified.

Your child's images and research data will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number.

WHAT ARE THE COSTS?

The cost of conventional imaging tests, which may include MRI, CT, Bone scan, Gallium scan, MIBG scan, and/or PET scan, is the responsibility of you and your insurance company. The whole-body MRI, which is an experimental imaging test, will be paid for by ACRIN. You and your insurance company are responsible for all costs that may result from any of these diagnostic tests, including the cost of standard needle or surgical biopsy, bone marrow aspiration, clinical follow-up, and any other follow-up tests and/or treatments that result from screening. In the case of injury or illness resulting from this study, emergency medical treatment is available but will

be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

In the case that anesthesia is requested by you or your child's physician, additional costs may be incurred, and should be discussed with the study doctor.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You or your child will receive no payment for taking part in this study.

WHAT ARE MY CHILD'S RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to have your child take part or your child may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which he/she is entitled.

A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your child's health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed by the site.)

For additional information about your child's health, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your child's rights as a research subject, you may contact:

(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

Visit the NCI's Web sites for comprehensive clinical trials information <http://cancertrials.nci.nih.gov>, <http://cancernet.nci.nih.gov>, or the American College of Radiology Imaging Network's website www.acrin.org.

CHILD ASSENT DOCUMENTATION

I certify that the study described above has been explained to the subject in terms that he/she could understand and that were appropriate to his/her age and ability to comprehend, and that he/she freely assented to participate in this study.

Investigator Signature

Date

Parent (or Legal Guardian) Signature

Date

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent for my child to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

FOLLOW-UP AT YEARS 1, 2, AND 3:

Yes, I give my permission for the study doctors to obtain follow-up information at year 1, 2, and 3.

No, I do not give my permission for the study doctors to obtain follow-up information at year 1, 2, and 3.

Parent (or Legal Guardian) Signature

Date

ACRIN 6660

WHOLE-BODY MRI IN THE EVALUATION OF PEDIATRIC MALIGNANCIES

SAMPLE CONSENT FOR RESEARCH STUDY—Participants 18 years of age and older

This is a clinical trial (a type of research study). Clinical trials include only participants who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need to Know,” is available from your doctor.

You are being asked to be in this study because you have a type of cancer that can spread to other areas of the body. Researchers are trying to find the best way to see if and where the cancer has spread (metastatic disease).

WHY IS THIS STUDY BEING DONE?

The standard tests that are used to determine the extent and spread of your disease are magnetic resonance imaging (MRI), computed tomography (CT) and bone scanning, gallium scanning, metaiodobenzylguanidine (MIBG) scanning, and/or positron emission tomography (PET) scanning. The purpose of this study is to determine if the newer imaging test referred to as whole-body MRI can detect the extent and spread of disease as accurately as the standard tests. The results of whole-body MRI will be compared with those of conventional imaging (standard studies) for detecting distant metastases.

Whole-body MRI is a diagnostic test that uses a large magnet to take pictures of the body with rapid imaging times. Up to now it has not been used routinely in the evaluation of all children with cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 226 participants age 21 years and younger will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following tests and procedures:

- Conventional Imaging Tests: May include MRI, CT, Bone Scan, Gallium Scan, MIBG Scan, and/or PET scan.
- Experimental Imaging Test: Whole-Body MRI.

Standard needle or surgical biopsy and/or bone marrow aspiration or clinical follow-up will be done as standard care to confirm diagnosis of metastatic disease.

The experimental whole-body MRI studies are conducted in the same way as the routine MRI studies except the overall time you will spend in the MRI unit is significantly shorter and no i.v. contrast is needed. The whole-body MRI will be performed at the time of initial diagnosis. For this test, you will lie in a long tube of the magnetic resonance scanner on your back for about 15 to 30 minutes.

HOW LONG WILL I BE IN THE STUDY?

The length of time you will be in the study will be six (6) months. During the follow-up time, you will undergo imaging tests and biopsies for the management of your specific disease. After the initial research imaging is done, your doctor will continue to follow how you are doing with your treatment and follow-up. Your information may be collected as part of clinical follow-up at years one (1), two (2), and three (3) from the time of your initial research imaging. Your doctor for the study will provide this information.

You can stop participating in this study at any time. However, if you decide to stop your participation in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While you are on the study, you are at risk for the side effects listed below. You should discuss these with the researcher and/or your regular doctor.

The side effects associated with the experimental imaging test are the same as those associated with the standard tests used for diagnosis. Because it is an additional test, the whole-body MRI increases the risk of false positive results, as any imaging test can; false positive results can cause anxiety or unnecessary biopsies.

Side Effects Associated with Whole-Body MRI

Likely:

The MRI scanner room is kept cool, and you may experience some discomfort from being cold, but you will be given a blanket. The scanner makes a loud knocking noise when it is taking pictures, but you will be given earplugs, or you may put on headphones and listen to the radio.

Less likely:

You may experience some claustrophobia or some anxiety about being in the long tube of the scanner. If you need to get out of the scanner at any time, the technologist can hear your request.

There is the risk of increased anxiety or stress associated with the whole-body MRI study demonstrating the possibility of tumor somewhere in your body. Some participants may be anxious regarding this uncertainty of test results. In addition, there is the risk that whole-body MRI study findings will lead to a need for more testing (such as x-rays, nuclear medicine scans, or biopsy) and that you will be found to have a more advanced stage of disease requiring more aggressive treatment.

Reproductive Risks:

Participants in this study must not be pregnant or nursing. Talk with your physician about the risks associated with pregnancy during cancer treatment.

ARE THERE POTENTIAL BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other children who have a similar disease in the future. If the whole-body MRI studies prove to be as accurate as the standard diagnostic procedures it will make the evaluation of children with this, or a similar disease, simpler and faster than with the current tests. The whole-body MRI may improve the accuracy of assessing the extent of disease of your tumor.

WHAT OTHER OPTIONS ARE THERE?

If you choose not to participate in this study your care will not be affected. All tests used in the study are available to patients without being registered on this protocol.

WHAT ABOUT CONFIDENTIALITY?

You understand that every attempt will be made by the investigators to keep all the information collected in this study strictly confidential, including your personal information. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN). All data sent to ACRIN over the Internet will be coded so that other people cannot read it. Your personal information may be disclosed if required by law.

You further understand that authorized representatives of ACRIN, the Food and Drug Administration (FDA), the National Cancer Institute (NCI), the local Institutional Review Board (IRB) and other groups or organizations that have a role in this study will have access to and may copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your images and research data will be kept permanently on file at ACRIN and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number.

WHAT ARE THE COSTS?

The cost of conventional imaging tests, which may include MRI, CT, Bone scan, Gallium scan, MIBG scan, and/or PET scan, is the responsibility of you and your insurance company. The whole-body MRI, which is an experimental imaging test, will be paid for by ACRIN. You and your insurance company are responsible for all costs that may result from any of these diagnostic tests, including the cost of standard needle or surgical biopsy, bone marrow aspiration, clinical follow-up, and any other follow-up tests and/or treatments that result from screening. In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed by the site.)

For additional information about your health, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

Visit the NCI's Web sites for comprehensive clinical trials information <http://cancertrials.nci.nih.gov>, <http://cancernet.nci.nih.gov>, or the American College of Radiology Imaging Network's website www.acrin.org.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

FOLLOW-UP AT YEARS 1, 2, AND 3:

Yes, I give my permission for the study doctors to obtain follow-up information at year 1, 2, and 3.

No, I do not give my permission for the study doctors to obtain follow-up information at year 1, 2, and 3.

Participant (or Legal Guardian) Signature

Date

APPENDIX II

ACRIN 6660: Whole-Body MRI for Pediatric Malignancies Eligibility Check

Institution # _____

Page 1 of 3

Case # _____ (to be provided upon activation)

The following questions will be asked at Study Registration:

- _____ 1. Institutional person registering case (initials only)
- _____ (Y) 2. Have all of the questions on the Eligibility Checklist been completed?
- _____ (Y) 3. Is the participant eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed (Must be prior to study entry)
- _____ 5. Participant’s Initials (Last, First)
- _____ 6. Verifying Physician (Site PI)
- _____ 7. Participant’s ID number (Do NOT utilize a medical record number or radiology-assigned number)
- _____ 8. Date of Birth (mm-dd-yyyy)
- _____ 9. Ethnic category
 - 1 Hispanic or Latino
 - 2 Not Hispanic or Latino
 - 9 Unknown
- _____ 10. Race (check all that apply):
 - American Indian or Alaskan Native
 - Asian
 - Black or African American
 - Native Hawaiian or other Pacific Islander
 - White
 - Unknown
- _____ 11. Gender
 - 1 Male
 - 2 Female
- _____ 12. Participant’s country of residence (if country of residence is *other, complete Q18*)
 - 1 United States
 - 2 Canada
 - 3 Other
 - 9 Unknown

- _____ 13. Zip Code (US residents)
- _____ 14. Participant's Insurance Status
- 1 Private insurance
 - 2 Medicare
 - 3 Medicare and Private insurance
 - 4 Medicaid
 - 5 Medicaid and Medicare
 - 6 Military or Veterans Administration
 - 7 Self-pay
 - 8 No means of payment
 - 9 Unknown/decline to answer
 - 0 Other
- _____ 15. Will any component of the participant's care be given at a military or VA facility?
- 1 No
 - 2 Yes
 - 9 Unknown
- _____ 16. Calendar Base Date (mm-dd-yyyy)
- _____ 17. Registration Date (mm-dd-yyyy)
- _____ 18. Other country, specify (completed only if Q12 is coded *other*)

Eligibility:

- _____ (Y) 19. Has a study-specific consent been signed by a parent (if the participant is < 18) or the participant (if participant is 18 or older)?
- _____ (Y) 20. Is the participant 21 years of age or younger?
- _____ (N) 21. Is the participant pregnant or nursing, or does she have reason to believe she may be pregnant?
- _____ 22. What is the type of proven or strongly suspected tumor?
Indicate tumor type:
- 1 Rhabdomyosarcoma
 - 2 Ewing's Sarcoma Family
 - 3 Neuroblastoma
 - 4 Non-Hodgkin's Lymphoma
 - 5 Hodgkin's Disease
 - 8 Other, specify _____
- _____ (N) 23. Has the participant had a previous malignancy?

_____ (N) 24. Does the participant have a known contraindication to MR or CT (i.e., ferrous vascular clips, pacemaker, etc.)?

_____ (Y/N) 25. Has the participant/parent (if participant is under the 18 years of age) agreed to PET imaging?

Signature of person responsible for data: _____

Signature of person entering data onto the web: _____

Date form completed (mm-dd-yyyy): _____

Appendix III: Participating Investigators and Institutions

<p>Nancy Rosen, MD and Sara J. Abramson, MD Memorial Sloan-Kettering Cancer Center Department of Radiology 1275 York Avenue New York, NY 10021 212-639-2184 Fax: 212-794 4010 Rosen1@mskcc.org; abramsos@mskcc.org;</p>	<p>Allison Friedmann, MD Harvard Medical School Massachusetts General Hospital 32 Fruit Street, White 246 Boston, MA 02114 617-726-2737 afriedmann@partners.org</p>
<p>Marco Amendola, MD Department of Radiology University of Miami Professional Arts Center, Suite 511 Miami, FL 33136 305-585-5057 bamendol@mediaone.net</p>	<p>Paul Babyn, MD The Hospital for Sick Children 555 University Avenue Toronto, Ontario M5G 1X8 416-813-5527 Fax: 416-813-5791 paul.babyn@sickkids.ca</p>
<p>Kimberly E. Applegate, MD, MS Health Services Research Riley Hospital for Children, 1053b 702 Barnhill Dr. Indiana University Medical Center Indianapolis, IN 46202-5200 317-274-2951 Fax: 317-274-2920 kiappleg@iupui.edu</p>	<p>Helen Nadel, MD British Columbia's Children's Hospital 4480 Oak Street Vancouver, BC Canada, V6H3V4 604-875-3034 hnadel@cu.bc.ca</p>
<p>Marta Hernanz-Schulman, MD Dept. of Radiology/Radiological Sciences Vanderbilt University Medical Center 1161 21st Ave. S D-1120 Medical Center North Nashville, TN 37232-2675 615-343-7684 marta.schulman@mcmail.vanderbilt.edu</p>	<p>John Cassese, MD Brown University Hasbro Children's Hospital 593 Eddy Street Providence, RI 02903 401-444-5184 jcassese@lifespan.org</p>
<p>Fredric Hoffer, MD, Co-investigator Pediatric Interventional Radiologist Department of Radiology, R-5438 Children's Hospital & Regional Medical Center 4800 Sand Point Way NE Seattle, WA 98105 206-987-2134 Fax: 206-987-2341 fred.hoffer@seattlechildrens.org</p>	<p>James Meyer, MD Department of Radiology Children's Hospital of Philadelphia (CHOP) Philadelphia, PA 19104 Phone: 267-426-7885 Fax: 267-426-7490 meyer@email.chop.edu</p>
<p>Marilyn Siegel, MD, Principal Investigator Mallinckrodt Institute of Radiology Washington University School of Medicine 314-454-6229 Fax: 314-454-2868 siegelm@mir.wustle.edu</p>	<p>J. Brad Wyly, MD, Co-investigator Egleston Children's Hospital 1405 Clifton Rd. NE Atlanta, GA 30322 Phone: 404-325-6407 Fax: 404-315-2216 brad.wyly@choa.org</p>

<p>Geetika Khanna, MD Assistant Professor Department of Radiology University of Iowa Hospitals and Clinics 200 Hawkins Drive Iowa City, IA 52242 Phone: 319-356-1594 Fax: 319-356-2220 geetika-khanna@uiowa.edu</p> <p>Yutaka Sato, MD – Site Co-Investigator University of Iowa 319-356-1955 yutaka-sato@uiowa.edu</p>	<p>Joseph Mammone, MD Cancer Institute of New Jersey 1 Robert Wood Johnson Place Dept. of Radiology, MEB #404 New Brunswick, NJ 08903 732-235-7721 germaine46@comcast.net</p>
<p>Cynthia Rigsby, MD Children’s Memorial Hospital Chicago, IL 60614 Phone: 773-880-3540 Fax: 773-880-3517 crigsby@childrensmemorial.org</p>	<p>Craig Barnes, MD Wake Forest University School of Medicine Department of Radiology Winston-Salem, NC 27157 336-716-2463 Fax: 336-716-2029 cebarnes@wfubmc.edu</p>
<p>Matthias H. Schmidt, MD IWK Health Centre 5850 University Avenue Halifax, Nova Scotia B3J 3G, Canada 902-470-7821 Fax: 902-470-7463 matthias.schmidt@iwk.nshealth.ca</p>	<p>Mary McCarville, MD St. Jude Children’s Research Hospital Department of Radiology Imaging 332 N. Lauderdale Memphis, TN 38105 901-495-2399 Fax: 901-527-0054 Beth.McCarville@stjude.org</p>
<p>Johan G. Blickman, MD. PhD UMC Nijmegen Geert Grooteplein 10 6500 HB Nijmegen, The Netherlands 31-24-3614546 j.blickman@rad.umcn.nl</p>	<p>Dilip Gole, MD Nemours Children’s Hospital Pediatric Radiology 807 Children’s Way Jacksonville, FL 32247 (904) 858-3868 dgole@nemours.org</p>
<p>Jeanne Hill, MD Medical University of South Carolina 171 Ashley Avenue Charleston, SC 29425 hillj@musc.edu</p>	<p>Carol Portwine, MD McMaster University 1200 Main Street E. Hamilton, ON L8N3Z5 (905) 521-2100, ext. 73428 portwc@mcmaster.ca</p>
<p>Laura Fenton, MD The Children’s Hospital of Denver Department of Radiology, B125 Denver, CO 80218 Phone: 303-764-8431 Fax: 303-764-8669 fenton.laura@tchden.org</p>	

APPENDIX IV

SPECIFIC CT, MRI, SCINTIGRAPHY, AND FDG-PET PROTOCOLS

Details of the CT, MRI, Scintigraphy, and PET techniques are available on the ACRIN web site at (http://www.acrin.org/6660_protocol.html). For more detailed information, contact Anthony Levering at alevering@phila.acr.org.

APPENDIX V

Radiation Dose Estimates for MDP, Gallium, MIBG, and FDG

From: Stabin MG, Gelfand MJ, Dosimetry of pediatric nuclear medicine procedures. QJ Nucl Med 1998; 42:93-112.

These are only estimates; we expect your institution will have its own dosimetry. You may wish to submit your institution's dosimetry to your IRB.

Table I: Radiation dose estimates for ^{99m}Tc-MDP by intravenous injection

	Newborn	1-year old	5-year old	10-year old	15-year old	Adult
Estimated weight (kg)	3.2	10.2	18.5	32.4	55.5	70
Administered activity (mCi), based on recommended dose of 280 μ Ci/kg (minimum dose 2.5 mCi)	2.5	2.9	5.2	9.1	15.5	19.6
Effective Dose (ED) (rem)	0.58	0.28	0.27	0.31	0.34	0.34

Table II: Radiation dose estimates for ⁶⁷Ga-citrate by intravenous injection

	Newborn	1-year old	5-year old	10-year old	15-year old	Adult
Estimated weight (kg)	3.2	10.2	18.5	32.4	55.5	70
Administered activity (mCi), based on recommended dose of 140 μ Ci/kg (minimum dose 1.25 mCi)*	1.25	1.4	2.6	4.5	7.8	9.8
Effective Dose (ED) (rem)	5.5	2.5	2.9	3.4	3.5	3.6

* Alternate minimum suggested doses (mCi): Newborn, 0.25; 1-year-old, 0.4; 5-year-old, 0.76; 10-year-old, 1.3; 15-year-old, 2.2; adult, 3.0 (personal communication, Brad Wyly).

Table III: Radiation dose estimates for ¹²³I-MIBG by intravenous injection

	Newborn	1-year old	5-year old	10-year old	15-year old	Adult
Estimated weight (kg)	3.2	10.2	18.5	32.4	55.5	70
Administered activity (mCi), based on upper range of recommended dose of 140 µCi/kg (minimum dose 1.0 mCi)	1.0	1.4	2.6	4.5	7.8	9.8
Effective Dose (ED) (rem)	0.53	0.35	0.37	0.43	0.61	0.60

Table IV: Radiation dose estimates for ¹³¹I-MIBG by intravenous injection

	Newborn	1-year old	5-year old	10-year old	15-year old	Adult
Estimated weight (kg)	3.2	10.2	18.5	32.4	55.5	70
Administered activity (mCi), based on recommended dose of 1 µCi/kg (<u>maximum</u> dose 1.0 mCi)	0.04	0.14	0.26	0.45	0.78	0.98
Effective Dose (ED) (rem)	0.31	0.37	0.39	0.43	0.57	0.55

Table V: Radiation dose estimates for ¹⁸F-FDG by intravenous injection

	Newborn	1-year old	5-year old	10-year old	15-year old	Adult
Estimated weight (kg)	3.2	10.2	18.5	32.4	55.5	70
Administered activity (mCi), based on recommended dose of 140 µCi/kg (minimum dose 1.0 mCi and maximum dose 10 mCi)	1.0	1.4	2.6	4.5	7.8	9.8
Effective Dose (ED) (rem)	0.86	0.49	0.56	0.63	0.86	0.88

APPENDIX VI: Staging Systems

**Table 6.1 Intergroup Rhabdomyosarcoma Study Staging:
Surgical-Pathologic Grouping System**

Stage	Extent of Disease
I.	Localized tumor, completely resected
	A. Confined to the organ of origin
	B. Infiltration outside organ; regional nodes not involved
II	Compromised or regional resection of three types:
	A Grossly resected tumor with microscopic residual
	B Regional disease, completely resected, in which lymph nodes may be involved and/or tumor extension into adjacent organ may be present
	C Regional disease or involved lymph nodes, macroscopically resected but with evidence of microscopic residual
III	Incomplete resection or biopsy with macroscopic residual tumor
	A. Localized or locally extensive tumor, gross residual disease after biopsy only
	B. Localized or locally extensive tumor, gross residual disease after major resection (>50% debulking)
IV	Distant metastases present at diagnosis

Table 6.2. International Neuroblastoma Staging System (INSS)

Stage	Definition
1	Localized tumor with complete resection, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically
2A	Localized tumor with incomplete gross excision; representative ipsilateral nonadherent lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision, with representative ipsilateral nonadherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically.
3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement.
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow. Bone marrow involvement should be minimal (<10% of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate). Limited to infants < one year of age

Table 6.3. Ann Arbor Staging Classification of Hodgkin Disease

Stage	Criteria
I	Involvement of a single lymph node region
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement

Note: E = extralymphatic site, S = splenic involvement. The absence or presence of fever, night sweats, and unexplained loss of 10 percent or more of body weight in the 6 months prior to diagnosis are denoted by the suffix letters A or B, respectively.

Table 6.4. St. Jude Staging System for Non-Hodgkin's Lymphoma

Stage	Criteria
I	A single tumor (extranodal) or single anatomic site (nodal), excluding mediastinum or abdominal
II	<ul style="list-style-type: none">○ A single tumor (extranodal) with regional node involvement○ Two or more nodal sites on the same side of the diaphragm○ To single (extranodal) tumors with or without regional node involvement on the same side of the diaphragm○ A primary gastrointestinal tract tumor, usually ileocecal, with or without associated mesenteric nodes
III	<ul style="list-style-type: none">○ Two single tumors (extranodal) on opposite sides of the diaphragm○ Two or more nodal areas above and below the diaphragm○ All primary intrathoracic tumors (mediastinal, pleural, thymic)○ All extensive primary intra-abdominal disease○ All paraspinal or epidural tumors, regardless of other tumor site(s)
IV	Any of the above with initial central nervous system (CNS) or bone marrow involvement