



Pediatric Brain Tumor Consortium Neuroimaging Center

Manual of Operations

Boston Children's Hospital



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| Form 7 | Retired: No longer in use |
| Form 8 | Retired: No longer in use |
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| Form 10 | Retired: No longer in use |
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FORMS LEGEND [Legacy and current forms in use] Continued

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| Form 27 | ADC Histogram Analysis |
| Form 28 | MRI Brain Permeability |
| Form 29 | ADC Histogram Quality Assurance |
| Form 30 | sFDM QA & Data Form |
| Form 32 | 026 Quality Assurance Form |
| Form 33 | Serial Tumor Measurements |
| Form 34 | Medulloblastoma Evaluation |
| Form 35 | Post Radiation Assessment |

I. Overview and Goals

The Pediatric Brain Tumor Consortium (PBTC) is a multidisciplinary cooperative research organization devoted to the study of correlative tumor biology and new therapies for primary CNS tumors of childhood. Its mission is to contribute rapidly and effectively to the understanding and cure of these tumors through the conduct of multi-center, multidisciplinary, innovative studies with designs and analyses based on uniformly high quality statistical science. While the primary mission of the PBTC is to identify through laboratory and clinical science superior treatment strategies for children with brain cancers, the PBTC investigators recognize their profound responsibility to meet the special needs of the children and families as they face this enormous challenge. Members are committed to working within their institutions and communities to improve support services and follow up care for these patients and their families.

The goals of the PBTC Neuroimaging Center (NIC) are:

- To provide leadership in the diagnostic imaging component of all clinical PBTC protocols including the development, implementation and / or coordination of all current and future research protocols for diagnostic imaging studies. These include but are not limited to MRI, MR diffusion, MR perfusion, MR spectroscopy, CT and PET;
- To direct quality assurance activities for the neuroimaging studies including the oversight of compliance with imaging protocols and assessments of diagnostic image quality, data integrity and storage/retrieval;
- To provide centralized review and interpretation of all diagnostic neuroimaging studies and analyze CT, MRI, MRS, PET and other images to generate summary data that will be provided to the Operations and Biostatistics Center (OBC) for statistical analysis;
- To develop a correlative imaging research plan related to the novel therapeutic interventions of the PBTC;
- To ensure PBTC's ability to incorporate imaging endpoints in its overall research program;
- To oversee cross-platform translations for comparative analyses of MRI, MRS, and PET studies.

II. Organization

The overall organization of the Pediatric Brain Tumor Consortium (PBTC) is outlined in Figure 1. The consortium includes 11 participating Institutions and a special member (Neurooncology Branch NCI/NINDS), for the recruitment of patients into PBTC protocols, an Operation and Biostatistics Center, a Neuroimaging Center, and Central Laboratories. The Steering Committee is the primary decision-making body for the study with scientific oversight provided by an external Scientific Advisory Board. The work of the Consortium is accomplished through several ad-hoc and standing committees. Specifically, the Neuroimaging Committee (NC) is composed of one neuroradiologist from each participating institution and the PI of the NIC, Dr. Tina Young Poussaint. In addition there are external and internal liaisons on the committee. Under the leadership of Dr. Poussaint, the NC is responsible by consensus for the development of clear and standard procedures for the performance of all PBTC MR Neuroimaging studies across the sites and for all MR neuroimaging quality control procedures. In addition, the NC reviews imaging study data quality reports on a regular basis, provides recommendations regarding possible neuroimaging research questions that may be appropriate to be considered in relevant treatment protocols; and assists in the evaluation of research neuroimaging protocol feasibility, methods, and scientific merit. A PET investigator committee consisting of one PET investigator per site, provides input regarding PET QA, PET analyses, protocols, radiopharmaceuticals and PET research projects.

Figure 1 presents the PBTC organizational structure. Table 1 presents the MR Equipment at each site. Figure 2 presents the organizational structure of the NIC. Figure 3 presents the organizational structure of the Institutional Centers for Clinical and Translational Research at Boston Children's Hospital. Table 2 presents the PET Equipment at each site. Table 3 lists the PIs at each respective site. Table 4 lists the CRAs at each site. Table 5 lists the PET and MR QA contacts at each site.

Figure 1: Pediatric Brain Tumor Consortium Organization



PBTC Regulatory, Clinical and Scientific Infrastructure

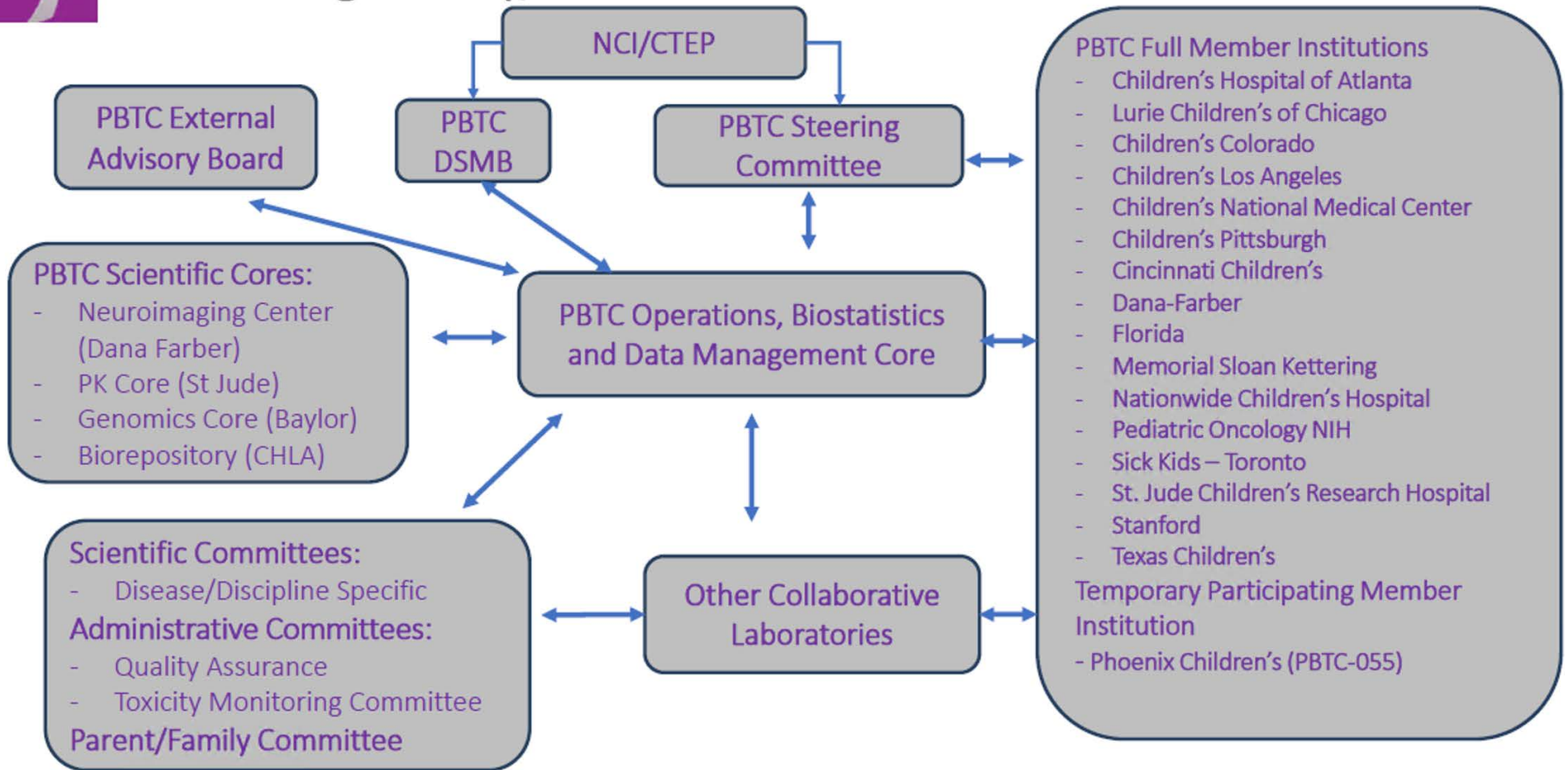


Figure 2: Organizational Structure of the NIC

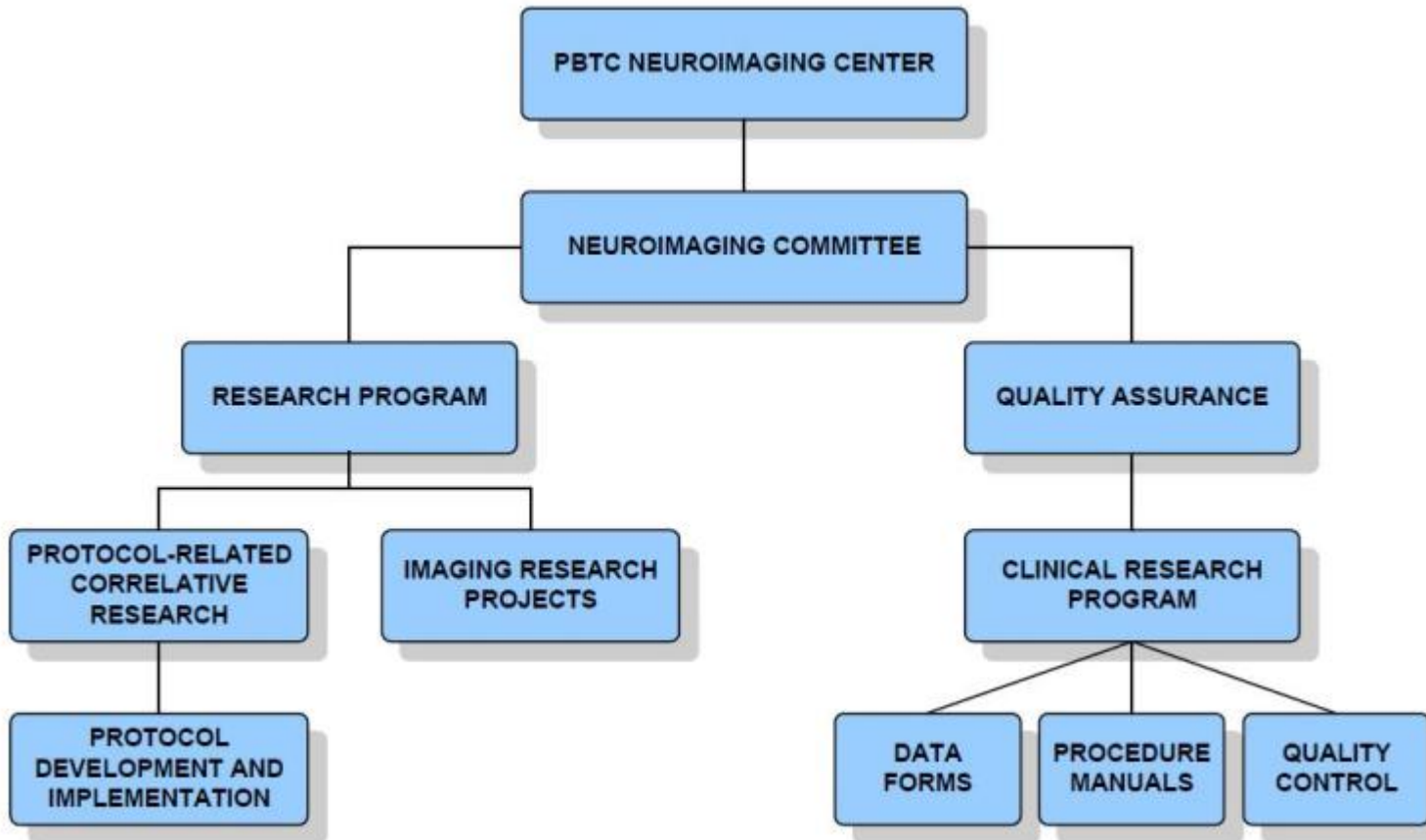
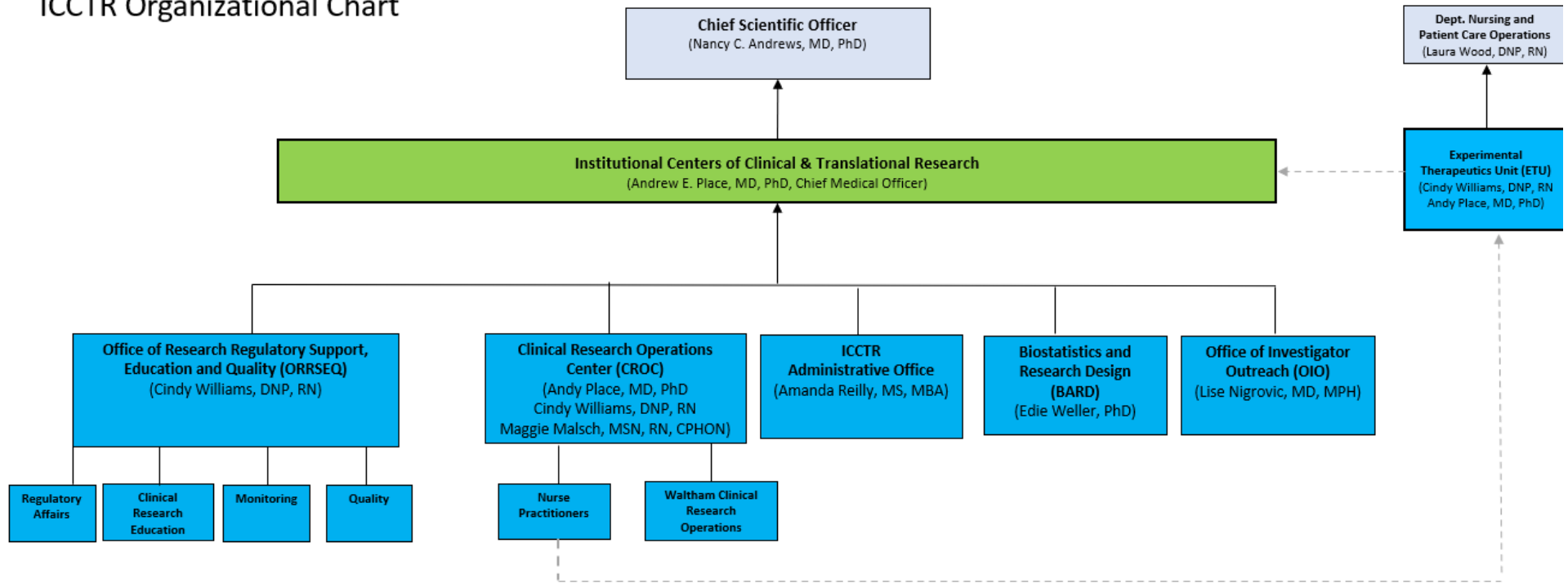


Figure 3:

ICCTR Organizational Chart



Boston Children's Hospital
 Institutional Centers for Clinical
 and Translational Research

Table 1: PBTC NIC MR Equipment List

| Site Code | Institution | Contact Name | Personnel | Contact Telephone | Contact Email |
|-----------|---|--|--|--|--|
| 11 | Children's National Medical Center, Washington, DC | Gilbert Vezina, MD Deena Brooks Christine Harris | MR Physician MR Technologist MR supervisor | 202-476-2389 202-476-3865 202-476-2941 | gvezina@cnmc.org dpprooks@cnmc.org |
| 14 | Boston Children's Hospital Dana Farber Cancer Center Boston, MA | Robert Mulkern, PhD Diane Biagiotti | MR Physicist MR Technologist | 617-355-3737 617-355-5154 | robert.mulkern@childrens.harvard.edu diane.allen@childrens.harvard.edu |
| 15 | Children's Hospital Pittsburgh of UPMC Pittsburgh, PA | Ashok Panigrahy, MD Dennis Willaman | MR Physician MR Technologist | 412-692-5510 412-693-3038 | ashok.panigrahy@chp.edu dennis.willaman@chp.edu |
| 16 | St Jude Children's Research Hospital Memphis, TN | Zoltan Patay, MD Kendri Herring Puneet Bagga (Soectroscopy) | MR Physician MR Supervisor | 901-595-2718 901-595-2013 901-595-4118 | zoltan.patay@stjude.org kendri.herring@stjude.org Puneet.Bagga@stjude.org |
| 18 | Texas Children's Hospital at Baylor Houston, TX | Nelish Desai, MD Joseph O Grigg | MR Physician MRI Adv Spec | 832-824-7237 832-824-5343 | nkdesai@texaschildrens.org jogrigg@texaschildrens.org |
| 20 | National Institutes of Health Bethesda, MD | Eva Baker, MD, PhD Baehr (RT/MRI) John Gold | MR Physician MR Supervisor | 301-594-6175 301-402-5586 301-402-5586 | bakere@mail.nih.gov baehrr@mail.nih.gov john.glod@nih.gov |
| 21 | Lurie Children's Hospital of Chicago Chicago, IL | Susan Palasis, MD Georgiena Prevett Christina Sammet, Ph.D (Spectroscopy) | MR Physician MR Manager Imaging Physicist | 312-227-3488 312-227-3393 312-277-3393 | spalasis@luriechildrens.org gprevett@luriechildrens.org csammet@luriechildrens.org |
| 22 | Cincinnati Children's Hospital Medical Center Cincinnati, OH | Blaise Jones, MD Kim Cecil, PhD Julie Young Jean A. Tkach, PhD (Spectroscopy) | MR Physician MR Technologist | 513-636-7475 513.636.8559 513-636-5805 513-636-7166 | blaise.jones@cchmc.org Kim.Cecil@cchmc.org julie.young@cchmc.org jean.tkach@cchmc.org |
| 23 | Children's Hospital Los Angeles Los Angeles, CA | Marvin Nelson, MD Mohammed Dar Stefan Bluml, PhD (Spectroscopy) | MR Physician MR Technologist | 323-361-2411 323-361-2411 323-361-5730 | mdnelson@chla.usc.edu mdar@chla.usc.edu sbluml@chla.usc.edu |
| 24 | Memorial Sloan-Kettering Cancer Center, New York, NY | Sofia Haque, MD Thomas Mair | MR Physician MR Technologist | 212-639-7170 212-639-6342 | haques@mskcc.org mair@mskcc.org |
| 25 | Lucile Packard Children's Hospital at Stanford Palo Alto, CA | Kristen Yeom, MD Young Chang | MR Physician MRI Clinical Instructor | 650-721-2388 650-724-2676 | kyeom@stanford.edu ychang@stanfordchildrens.org |

| Site Code | Institution | Contact Name | Personnel | Contact Telephone | Contact Email |
|-----------|---|--|--|------------------------------|--|
| 27 | Children's Hospital of Colorado Aurora, CO | David Mirsky, MD Sarah Smith | MR Physician MR Technologist (Research) | 720-777-2317 720-777-6848 | David.mirsky@cuanschutz.edu Sarah.smith@childrenscolorado.org |
| 28 | Children's Healthcare of Atlanta Atlanta, GA | Nadja Kadom, MD – Egleston Jack Knight-Scott – Egleston (Spectroscopy) Nicole Chin – Egleston Cassandra Dike – Egleston Melissa Weisel - Egleston Adina Alazraki MD - Scottish Rite Trista Raymer - Scottish Rite Richard Joens - Scottish Rite (MR Spectroscopy) Lawrence.Matarutse - Scottish Rite | MR Physician – Egleston MR Technologist Egleston MR Technologist Egleston MR Technologist Egleston MR Physician – Scot Rite MR Technologist Scot Rite Research manager Scot Rite | 404-785-6650 | Jack.Knight-Scott@choa.org cassandra.dike@choa.org Melissa.weisel@choa.org adina.alazraki@choa.org Trista.raymer@choa.org Richard.jones@choa.org Lawrence.Matarutse@choa.org |
| 26 | University of Florida, Gainesville, Florida | Mehmet Albayram, MD | MR Physician | 352-265-0291 | Albaym@radiology.ufl.edu |
| 34 | Sick Kids, Toronto, Ontario | Birgit Ertl-Wagner, MD | MR Physician | 416.813.5470 | BirgitBetina.Ertl-Wagner@sickkids.ca |
| 35 | Nationwide Children's Hospital, Columbus, Ohio | Aaron McAllister, MD | MR Physician | 614-722-5703 | Aaron.McAllister@nationwidechildrens.org |

Table 1a: PBTC NIC MR Equipment List

| Site Code | Institution | Equipment Vendor/Model* | Software Version | Contrast |
|-----------|---|--|---|---|
| 11 | Children's National Medical Center Washington, DC | GE Discovery 450 (1.5T) GE Optima 450W (1.5T) GE Discovery 750 (3.0T) | GE Discovery 450 (1.5T) - DV 26.0 GE Optima 450W (1.5T) - DV 26.0 GE Discovery 750 (3.0T) - DV 26.0 | Optimark 0.2 ml/Kg Gadavist 0.2 ml/Kg |
| 14 | Boston Children's Hospital Boston, MA | Siemens 3T Siemens 1.5 T | 15.0 VB17 VB17 | Gadavist 0.2 ml/Kg |
| 15 | Children's Hospital Pittsburgh of UPMC Pittsburgh, PA | GE 1.5T (2) GE 3.0T (1) Siemens Skyra (1) | 16.0 16.0 Not Available | Multihance 0.2 ml/Kg |
| 16 | St Jude Children's Research Hospital Memphis, TN | Siemens Avanto (1) Fit - 1.5T Siemens Prisma (2) 3.0T Siemens Skyra (1) 3.0T | Avanto Fit - Syngo MR A13B Prisma (x2)-Syngo MR D13D Skyra-E11 | Gadavist 0.1 ml/Kg |
| 18 | Texas Children's Hospital at Baylor Houston, TX | Siemens Skyra 3T E11 Siemens Aera 1.5T E11 Siemens Vida 3T XA10 Siemens Sola 1.5T XA10 Philips Ingenia 1.5T R5.6 | Manufacturer supplied software | Gadavist 0.1 ml/Kg |
| 20 | National Institutes of Health Bethesda, MD | Philips Achieva 3T, Philips Achieva 1.5T, Siemens Aera 1.5T, Siemens MMR 3T, Philips Ingenia Elition 3T | Philips: 5.7.1 Siemens: numaris/4 syngo MR e11 | Multihance 0.2 ml/Kg Prohance 0.2 ml/Kg Gadavist 0.1 ml/Kg (Depends on clinical or research study and exam type.) |
| 21 | Lurie Children's Hospital of Chicago Chicago, IL | Siemens Vida 3T GE Architect 3T | Siemens VE11 Syngo MR D13 Numaris/4 1.5T Version 23 | Gadavist 0.1ml/kg |
| 22 | Cincinnati Children's Hospital Medical Center Cincinnati, OH | GE 3T Architect (1), Philips 1.5T Ingenia (4), Philips 1.5T Ambition (1), Philips 3T Ingenia (1) | GE DV29 Philips R5.5.2 | Dotarem 0.2 ml/Kg |
| 23 | Children's Hospital Los Angeles Los Angeles, CA | Signa 9.1 M4 Philips (1.5T) Philips (3.0T) | Phillips 5.3 | Gadavist 0.1 ml/Kg |

Table 1a: PBTC NIC MR Equipment List

| Site Code | Institution | Equipment Vendor/Model* | Software Version | Contrast |
|-----------|--|--|---|--|
| 24 | Memorial Sloan-Kettering Cancer Center New York, NY | GE Signa 750W GE Signa 1.5T GE 450W GE 750 3T | DV26 DV29 MP26 | Gadavist 0.5 ml/Kg |
| 25 | Lucile Packard Children's Hospital at Stanford Palo Alto, CA | MR1 450W 1.5T MR2 750 3T MR3 750 3T | DV26 - DV28 | Multihance 0.1 ml/Kg Gadavist 0.1 ml/Kg |
| 27 | Children's Hospital of Colorado Aurora, CO | (MR11) Philips Elition 3T | MRI 1, 2, 3, and 4 all have software 5.6.1 | Multihance 0.2 ml/kg |
| 28 | Children's Healthcare of Atlanta Atlanta, GA | Egleston: Siemen Vida 3T Siemens Aera 1.5T Siemens AvantoFit 1.5T Scottish Rite: Siemens Prisma Fit Philips Ingenia Siemens Avanto Siemens Skyra | Egleston: Vida - XA20 Aera - E11E AvantoFit - E11C Scottish Rite: Prisma - VE11C Ingenia - 5.6.1.2 Avanto - VE11E Skyra - VE11E | Gadavist 1.5 ml/kg Gadavist 0.1 ml/kg |
| 26 | University of Florida, Gainesville, Florida | Siemens Verio 3T Siemens Avanto 1.5 T | Syngo MR B19DHHS | Gadavist 0.1 ml/kg |
| 34 | Hospital for Sick Kids, Toronto, Ontario | Siemens 3T Skyra installed 2017, Siemens 3T Skyra installed 2016, Philips 3T Achieva installed 2007; Philips 1.5T Achieva, installed 2007, upgraded 2018 Siemens 1.5T AvantoFit, installed 2013 | Siemens 3T Skyra, V 11 E Siemens 3T Skyra, V 11 E Philips 3T Achieva; 5.3.1.4 Philips 1.5T Achieva, , upgraded 2018, 5.3.1.3 Siemens 1.5T AvantoFit Software V 11 B (*) | Gadavist 0.1 ml/kg |
| 35 | Nationwide Children's Hospital, Columbus, Ohio | Siemens 3T Skyra Siemens 3T Prisma Siemens 3T Vida GE 3T 750 GE 1.5T HDX Siemens/IMRIS 1.5T Espree GE 1.5T Signa HD | Siemens 3T Skyra – E11C Siemens 3T Prisma - E11C Siemens 3T Vida – XA11B GE 3T 750 – DV29 GE 1.5T HDX – HD23 Siemens/IMRIS 1.5T Espree - B19 GE 1.5T Signa HD – HD23 | Gadavist 0.1 ml/kg |

Table 1a: PBTC NIC MR Equipment List

| Site Code | Institution - ASL Information | Equipment Vendor/Model* ASL Information | Pulse Sequence Indications | 1. Clinical/Research/Both? 2. Routine for Brain Tumors? |
|-----------|--|---|--|--|
| 11 | Children's National Medical Center Washington, DC | GE Discovery 450 (1.5T) GE Optima 450W (1.5T) GE Discovery 750 (3.0T) | 3DASL DV.26 To access vascularity | Clinical Yes |
| 14 | Boston Children's Hospital Boston, MA | Siemens 3T | pcastle V.17 tumors | Clinical Yes |
| 15 | Children's Hospital Pittsburgh of UPMC Pittsburgh, PA | GE 1.5T (2) SIEMENS SKYRA GE 3T DISCOVERY | PCASL 16 STROKE, TUMOR, VASCULAR DISEASE | Both Yes |
| 16 | St Jude Children's Research Hospital Memphis, TN | Siemens Avanto (1) Fit - 1.5T Siemens Prisma (2) 3.0T Siemens Skyra (1) 3.0T | PASL Non-contrast vessel evaluation | Both Yes |
| 18 | Texas Children's Hospital at Baylor Houston, TX | Siemens 3T Skyra Siemens 3T Vida | PCASL, PICORE, FAIR Tumor, stroke, Moyamoya | Both Yes |
| 20 | National Institutes of Health Bethesda, MD | ASL not acquired | None | None |
| 21 | Lurie Children's Hospital of Chicago Chicago, IL | 3T Vida PCASL 3T Skyra PASL 1.5T Aera PASL | 3T Vida PCASL 3T Skyra PASL 1.5T Aera PASL Epilepsy, HIE, Stroke | Clinical No |
| 22 | Cincinnati Children's Hospital Medical Center Cincinnati, OH | GE 1.5T GE 3T Philips 1.5T Philips 3T | GE : 3D spiral ASL (DV29) Philips : 2D pCASL (R5.7.2) Majority of brain applications (e.g. stroke, seizure, etc). | Both Yes |
| 23 | Children's Hospital Los Angeles Los Angeles, CA | Philips (3.0T) | PCASL 5.3 Perfusion | Both No |
| 24 | Memorial Sloan-Kettering Cancer Center New York, NY | Both 1.5T and 3T | 3D ASL Spiral | Clinical No |
| 25 | Lucile Packard Children's Hospital at Stanford Palo Alto, CA | 1.5T Signa Artist 3.0T 750 Discovery 3.0T Signa Architect | GE Standard sequence DV26-DV28 Tumor, Moya Moya, Stroke | Both Yes |
| 27 | Children's Hospital of Colorado Aurora, CO | Philips Ingenia 3T Philips Ingenia 3T Philips Elition 3T | 3D SE GraSE Software: 5.6.1 Stroke, Tumor, Inpatient Seizure, any MRI Brain ordered with a MRA or MRV | Both Yes |

Table 1a: PBTC NIC MR Equipment List

| Site Code | Institution - ASL Information | Equipment Vendor/Model* ASL Information | Pulse Sequence Indications | 1. Clinical/Research/Both? 2. Routine for Brain Tumors? |
|-----------|---|--|---|--|
| 28 | Children's Healthcare of Atlanta Atlanta, GA | Egleston: Siemen Vida 3T Siemens Aera 1.5T Siemens AvantoFit 1.5T | Egleston: Vida - XA20 pASL and pCASL Aera - E11E/AvantoFit - E11C pASL Stroke, Seizure, Sickle Cell, Tumor/Mass, Brain Trauma, | Both Yes |
| | | Scottish Rite: Philips Ingenia 3T | 3D GRASE with PCASL prep. Software 5.6.1.2 Moya-Moya, EDAS | Both No |
| 26 | University of Florida, Gainesville, Florida | ASL not acquired | None | None |
| 34 | Hospital for Sick Kids, Toronto, Ontario | ASL not acquired | None | None |
| 35 | Nationwide Children's Hospital, Columbus, Ohio | Siemens Skyra 3T Siemens Prisma 3T Siemens Vida 3T GE 750 3T GE HDX 1.5T | PACSL- Siemens software XA11B ASL -GE DV26 Tumors Perfusion abnormalities (hemiplegic migrains, AVMs, moya-moya, etc) | Both Yes |

Table 2: PBTC NIC PET Equipment List

SECTION A: Equipment

| Site Code | Institution | Equipment Vendor/Model | Contact Name | Personnel | Contact Telephone | Contact Email |
|-----------|---|----------------------------------|---|---|--|--|
| 11 | Children's National Medical Center Washington, DC | GE Discovery 690 PET/MDCT | Catalina Kovats, MD Sunil Valaparla Vyas Pranav, MD Fricke Stanley | PET Physician PET physicist PET Physician PET Physicist | 202-476-5075 202-476-6153 202-476-5630 202-476-6153 | ckovats@childrensnational.org svalaparla@childrensnational.org pvyas@childrensnational.org sfricke@cnmc.org |
| 14 | Boston Children's Hospital Dana Farber Cancer Center Boston, MA | Siemens mCT 40 PET/CT | Stephan Voss, MD Da Zhang Xinhua Cao, PhD Joanne Louis, CNMT Vicky Kourmouzi, CNMT, MSF | PET Physician PET Physicist Computer Specialist Chief Technologist – Nuclear Med Assistant Chief Technologist – Nuclear Medicine Specialist | 617-355-8317 617-355-5563 617-355-5820 | Stephan.voss@childrens.harvard.edu Da.Zhang@childrens.harvard.edu xinhua.cao@childrens.harvard.edu Joanne.Louis@childrens.harvard.edu Vasiliki.Kourmouzi@childrens.harvard.edu |
| 15 | Children's Hospital Pittsburgh of UPMC Pittsburgh, PA | GE Discovery DVCT PET/CT | Jennifer Shoaf CNMT Shyam M. Srinivas, MD, PhD | Nuclear Imaging Supervisor PET Physician | 412-692-9518 412-647-0104 | jennifer.conver@chp.edu srinivassm@upmc.edu |
| 16 | St Jude Children's Research Hospital Memphis, TN | GE Discovery 690 | Christiane Burton Nancy Foster Nathan Artz, PhD | Computer Specialist PET Physicist | 901-595-3347 | Christiane.Burton@STJUDE.ORG Nancy.foster@stjude.org Nathan.Artz@stjude.org |
| 18 | Texas Children's Hospital at Baylor Houston, TX | Philips Vereos Digital PET/CT | Andrew Sher, MD | PET Physician | 832-824-7237 | acssher@texaschildrens.org |
| 20 | National Institutes of Health Bethesda, MD | Siemens MCT PET/CT (2) | Peter Herscovitch, MD Craig Barker, PhD Charles Fraser | PET Physician PET Physicist Computer Specialist | 301-451-4248 301-451-3558 301-451-3591 | pherscovitch@cc.nih.gov cbarker@nih.gov cfraser@cc.nih.gov |
| 21 | Lurie Children's Hospital of Chicago Chicago, IL | GE PET/CT Discovery 690 12123PT6 | Paige Nelson Susan Palasis Carla Quijano, MD Nicole murphy, MS, DABR | Research Coordinator PET Physician PET Physician Imaging Physicist | 312-2273479 312-227-3488 312-227-4500 312-227-3397 | pnelson@luriechildrens.org spalasis@luriechildrens.org cquijano@luriechildrens.org nmurphy@luriechildrens.org |
| 23 | Children's Hospital Los Angeles Los Angeles, CA | Philips/Gemini GXL16 PET/CT | Fariba Goodarzian, MD | PET Physician | 323-361-4162 | fgoodarzian@chla.usc.edu |

| Site Code | Institution | Equipment Vendor/Model | Contact Name | Personnel | Contact Telephone | Contact Email |
|-----------|---|---|--|---|--|--|
| 24 | Memorial Sloan-Kettering Cancer Center New York, NY | General Electric PET/CT | Neeta Pandit-Taskar, MD Adam Kesner Assen Kirov | PET Physician PET Physicist PET Physicist | 212-639-7372 212-639-6371 212-639-7126 | Pandit-n@mskcc.org kesnera@mskcc.org kirova@mskcc.org |
| 25 | Lucile Packard Children's Hospital at Stanford Palo Alto, CA | GE DMI | Helen Nadel, MD Andrei Iagaru, MD Craig Levin, PhD | PET Physician PET Physician PET Physicist | 650-721-5083 650-725-8263 650-736-7211 | hnael@stanford.edu aiagaru@stanford.edu cslevin@stanford.edu |
| 27 | Children's Hospital of Colorado Aurora, CO | Siemens Biograph Vision 600 | Nicholas Stence, MD Sarah Oeth | PET Physician PET Technologist | 720-777-8571 720-777-8631 | Nicholas.Stence@ucdenver.edu sarah.oeth@childrenscolorado.org |
| 28 | Children's Healthcare of Atlanta Atlanta, GA | Siemens Biograph 64, Siemens 128 slice PET Vision | Adina Alazraki, MD Cassandra Dike | PET Physician PET Supervisor | 404-785-0474 | alazraki@choa.org Cassandra.dike@choa.org |
| 26 | University of Florida, Gainesville, Florida | | Dhanashree Rajderkar, MD Stephanie Leon, PhD | PET Physician PET Physician | 352-265-0291 352-594-2492 | Rajdda@radiology.ufl.edu LEONS@radiology.ufl.edu |
| 34 | Hospital for Sick Kids, Toronto, Ontario | GE Discovery MI | Amer Shammass, MD Reza Vali, MD Susan Mcquattie | PET Physician PET Physician Lead PET Technologist | 416.813.7510 | amer.shammass@sickkids.ca reza.vali@sickkids.ca susan.mcquattie@sickkids.ca |
| 35 | Nationwide Children's Hospital, Columbus, Ohio | No new PET/CT equipment | Adam Bobbey, MD Laurie Gibson | PET Physician Nuclear Medicine Clinical Manager | 614-722-2350 614-722-9230 | Adam.Bobbey@nationwidechildrens.org Laurie.Gibson@nationwidechildrens.org |

Table 2: PBTC NIC PET Equipment List

SECTION B Radiopharmaceuticals

SECTION C Image Analysis Equipment

SECTION D Research Interests

| Site Code | Institution | Radiopharmaceuticals Used with Brain imaging | Image Analysis Equipment | Brain Imaging research at site unrelated to the PBTC |
|-----------|--|--|---|--|
| 11 | Children's National Washington, DC | FDG | GE AW workstation | Projects in fetal MRI, fMRI |
| 14 | Boston Children's Hospital Boston, MA | FDG, FLT, FDG | Hermes Medical Solution Workstation ECAT Software (CTI), Xeleris/AW (GE), Hermes, Siemens Leonardo/True D | Animal Micro PET, Epilepsy-spect Adult brain tumors. Central PET core lab for global multi-center trial of lapatinib in brain metastases in women with breast cancer |
| 15 | Children's Hospital Pittsburgh of UPMC Pittsburgh, PA | FDG | GE Discovery DVCT | Possible FLT in near future |
| 16 | St Jude Children's Research Hospital Memphis, TN | 11 C-MET-PET 18 F-FDG | Hermes Medical Solution Workstation | C-11 methionine uptake for CNS tumor survey Relation of histology to FDG uptake |
| 18 | Texas Children's Hospital at Baylor Houston, TX | FDG | MIM vista software Philips Portal | No participation in Brain imaging research prior to PBTC |
| 20 | National Institutes of Health Bethesda, MD | FDG, H2O, fdopa, fcway, flumazenil, nnc, leucine, dasb, fallypride, raclopride, methylreboxitine, DTBZ, FP-TZTP, FCWAY, arachidonic acid, docosahexaenoic acid, acetate Ga-68 DOTATATE | PACS | Stroke, epilepsy, Alzheimer's, Parkinson's, schizophrenia, depression, obsessive compulsive disorder, tumor, alcohol abuse, movement disorders, Fragile X |
| 21 | Lurie Children's Hospital of Chicago Chicago, IL | FDG | GE PET/CT Discovery 690 12123PT6 AW | N/A |
| 22 | Cincinnati Children's Hospital Medical Center Cincinnati, OH | F-18 FDG, Tc-99m-ECD, Tc-99m- HMPAO | Analyze 10, SPM, Brain Lab, MIM Neuro | Significant brain imaging research portfolio, to include, but not limited to, structural MRI, functional MRI, epileptogenic focus localization, dopamine transporter density |
| 23 | Children's Hospital Los Angeles Los Angeles, CA | F18-FDG | MIM for PET and MIBG Symbianet for MIBG cases | N/A |
| 24 | Memorial Sloan-Kettering Cancer Center New York, NY | FDG, FLT, and FACB | MIM Radiology & Nuclear Medicine software | F-choline in brain (PI at site is Kathryn Beall) |
| 25 | Lucile Packard Children's Hospital at Stanford Palo Alto, CA | FDG, FLT, Neuraceq, Vizamal | GE Advantage Windows | Amyvid (AV-45) |
| 27 | Children's Hospital of Colorado Aurora, CO | FDG | TeraRecon and SyngoVia | For PET, none |

| Site Code | Institution | Radiopharmaceuticals Used with Brain imaging | Image Analysis Equipment | Brain Imaging research at site unrelated to the PBTC |
|-----------|---|--|--|--|
| 28 | Children's Healthcare of Atlanta Atlanta, GA | FDG | PET/CT Whole body - Oncology PET/CT Skull to Mid-Thigh - Oncology PET/CT Brain - Epilepsy-Oncology | 1 research study - SISCOM (Subtraction Ictal Spect Co-registered to MRI) |
| 26 | University of Florida, Gainesville, Florida | FDG, FLT, and FACB | GE PET VCAR Hermes Medical Systems | F-choline in brain (PI at site is Kathryn Beall) |
| 34 | Hospital for Sick Kids, Toronto, Ontario | 18F-FDG | GE AW server | None |
| 35 | Nationwide Children's Hospital, Columbus, Ohio | NaF18, F18 FDG, Ga68 Dotatate | MM | None |

Table 3: PBTC Institutions and Principal Investigators

| | |
|--|--|
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| | |
|---|--|
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| | |
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Table 4: PBTC Clinical Research Associates/Nurses

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Table 5: PET and MR QA Contacts

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Table 5: PET and MR QA Contacts

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Table 5: PET and MR QA Contacts

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III. Neuroimaging Studies

This section outlines and provides an overview of the different types of neuroimaging studies that are used in various PBTC protocols. The NIC assists in therapeutic protocol development by providing standardized language describing diagnostic qualitative and quantitative neuroimaging procedures and their implementation in participating institutions. Protocols and implementation are developed by consensus and in collaboration with the Neuroimaging and PET Investigator Committees. The detailed procedures for standard sequences, contrast doses and infusion times, image data storage, image data transfer, tumor measurement and response criteria, and volumetric analysis can be found in each specific imaging study protocol on the website. A brief description of each study follows.

A. MRI: Standard Sequences

MRI is the primary neuroimaging modality used for monitoring the effects of the PBTC therapeutic protocols. MRI is sufficiently mature to allow for a standardization of imaging protocols between sites despite disparities between MRI manufacturers. The NIC staff provides each site with a minimum set of MRI sequences, which must be performed for inclusion into the database including T1, T2, FLAIR, gradient sequences and susceptibility weighted sequences. Standardization of all pulse sequence parameters including slice plane selection, slice thickness, in-plane matrices, spatial resolution, repetition times, echo times, and echo train lengths is mandated among the sites.

Data analysis of standard MR images includes tumor location, tumor signal characteristics, and presence of hemorrhage. Tumor volume is obtained from FLAIR or T2 sequences and T1 gadolinium sequences (enhancing and nonenhancing: cyst/necrosis) using the Vitrea™ workstation (Vital Images, Plymouth, MN) (See Form 1a). For leptomeningeal disease, tumor location, presence of disease (whether linear or nodular (single or multiple)) is recorded. (See form 6 and 9).

For hemorrhage assessment, presence of hemorrhage is recorded and an estimate of the percentage of hemorrhage in the tumor is determined and categorized as 0-25%, 26-50%, 51-75% and greater than 75%. The signal characteristics of the hemorrhage are determined on the following sequences: T1, T2, FLAIR, and diffusion, perfusion, gradient echo and susceptibility weighted series (See Form 1a).

B. CT

Parameters will be established for CT data acquisition for those PBTC protocols requiring CT imaging. Standardization of all parameters will be done. CT scans are done as needed for hemorrhage assessment in the acute setting (See Form 11).

C. MR Spectroscopy

MRS offers a noninvasive in vivo approach to biochemical analysis. MRS provides additional quantitative information regarding cellular metabolites since signal intensity is linearly related to steady-state metabolic concentration. MRS may detect cellular biochemical changes prior to the detection of morphological changes by MRI or other imaging modalities. Some of the more important applications of proton MRS in the assessment of CNS neoplasia at the current time are to evaluate cellular response to

therapy, to direct tissue biopsies, to plan surgical resections, to define disease extent and to differentiate tumor progression from treatment effects such as necrosis.

Single voxel MRS PRESS sequences has been required at all sites which can be substituted by multivoxel technique at sites with this capability. Please note all sites should do a screen save of the MRS spectrum with the ratios displayed on the image. In addition MRS raw data should be saved and transferred to the OBC (See MRS raw data transfer-Section 4C).

Calculation of MRS ratios includes NAA/tCr, choline/tCr, lipid/tCr. Other metabolites of interest include citrate, myoinositol, and taurine.

D. MR Diffusion

Diffusion imaging is standardized using single-shot echoplanar spin echo based diffusion sequences. MR diffusion has been useful in the characterization of tissue, tumor cellularity, tumor grading, tumor response to treatment and distinction of tissue types. Diffusion tensor imaging (DTI) provides visualization of fiber bundle direction and integrity which has applications including presurgical planning or coregistration of tractography data with radiosurgical planning and functional imaging MR data as well as assessing treatment-induced white matter changes.

Standardization of sequence parameters includes slice thicknesses, axial locations, spatial resolution, TE and b-factor values.

For standard MR diffusion, a region of interest is placed over the solid part of the tumor divided by the MR diffusion region of interest in the frontal white matter and the ratio value recorded. Coordination with region-of-interest (ROI) from the CBV map is done as necessary. For DTI, fractional anisotropy (FA), apparent diffusion coefficient (ADC) and RGB-orientation color maps are created using software created for this purpose using IDL (ITT Visual Information Solutions, Boulder, CO). TrackVis is used to visualize and analyze fiber track data from diffusion MR imaging. In selected protocols, ADC histogram analyses (providing volumetric assessment of tumor ADC) and functional diffusion map analyses are done.

E. MR Perfusion

MR perfusion imaging is currently being used to evaluate cerebral perfusion dynamics by analyzing hemodynamic parameters including relative cerebral blood volume, relative cerebral blood flow, and transit time, all as complementary to conventional MR imaging. The MRI perfusion data is analyzed using the method of Ostergaard et al developed at MGH, including maps of rCBV, rCBF, CBV corrected for permeability changes, and a T2-based permeability-surface area product measurement.

An MR perfusion region of interest is placed in the solid part of the tumor with highest CBV and divided by MR perfusion region of interest from the frontal white matter and the ratio value recorded.

Parameters for echoplanar gradient echo mode single-shot perfusion imaging are standardized.

MR permeability imaging with 3D axial T1 dynamic contrast enhanced sequences uses kinetic modeling yielding permeability (Kps) and CBV measurements. A modified Tofts model is used (2-compartment, bi-directional flux) to estimate both fractional blood volume (fBV) and microvascular permeability (Kps). DCE permeability MRI metrics also include the volume transfer constant between plasma and extravascular extracellular

space (K_{trans}), fractional blood-plasma volume (V_p), and the volume of the extravascular extracellular space per unit volume tissue (V_e)

F. Positron Emission Tomography (PET)

PET imaging is used for evaluation of drug distribution and metabolism, to assess metabolic activity in brain tumors, to assess tumor progression, radiation necrosis and treatment-associated changes in tumor metabolism.

Standard PET procedures are available for those sites having PET capabilities. As a high degree of anatomic localization is required, the PET images are co-registered with MRI data on a workstation used for registration and analysis (Hermes Medical Solutions, Stockholm, Sweden) and converted to Interfile 3.3 image format (See Form 4). Specific PET information is recorded by the site at submission of the PET study (See Form 14 PET support form).

G. PBTC Imaging Protocol Tables

Tables 6 and 7 below outline each PBTC study protocol and the neuroimaging studies that must be completed for that protocol. Study patients are scheduled for their procedure by the site P.I. and the requisition clearly marked to indicate that this is a PBTC study patient along with the PBTC Study Protocol Number in which the patient is enrolled. It should be noted that if more than one neuroimaging study is required and all sequences cannot be completed due to unforeseen circumstances, the priority of MR measurements are as follows: 1) standard MR sequences 2) MR diffusion, 3) MR perfusion, 4) and MR spectroscopy.

Table 6: PBTC Protocols [001 – 009]

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|-----------------|--|---|-----------------|---|
| PBTC-001 | A Pilot Study of Systemic and Intrathecal Chemotherapy followed by Conformal Radiation for Infants with Embryonal Intracranial Central Nervous System Tumors | None | Study completed | No correlative objective. Estimate PFS, pattern of failure. Central review of MRI scan at end of study |
| PBTC-002 | A Phase I Study of SU5416 in Pediatric Patients With Recurrent or Progressive Poor Prognosis Brain Tumors | <u>Stratum 1</u> : Patients not on enzyme-inducing anticonvulsant drugs <u>Stratum 2</u> : Patients receiving enzyme-inducing anticonvulsant drugs | Study completed | To identify the signal characteristics and biologic correlates of tumors after SU5416 treatment. |
| PBTC-003 | A Phase I Trial of Escalating Oral Doses of SCH 66336 in Pediatric Patients with Refractory or Recurrent Brain Tumors | None | Study completed | No correlative objective. MRI for response only. No central review. |
| PBTC-004 | A Phase I Study of Intrathecal Spartaject™-Busulfan in Children with Neoplastic Meningitis | None | Study completed | No correlative objective. MRI for response only with central review |
| PBTC-005 | A Phase I Trial of Temozolomide and O ⁶ -Benzylguanine in Pediatric Patients with Recurrent Brain Tumors | <u>Stratum 1</u> : patients previously not treated with RT or only focal RT <u>Stratum 2</u> : patients with prior craniospinal irradiation or myeloblastic therapy. | Study completed | No correlative objective. MRI for response only with central review |
| PBTC-006 | A Phase I/II Trial of STI571 in Children with Newly Diagnosed Poor Prognosis Brainstem Gliomas and Recurrent Intracranial Malignant Gliomas | <u>Stratum 1</u> : newly diagnosed localized brainstem tumors <u>Stratum 2A</u> : recurrent intracranial malignant gliomas - not using EIACD <u>Stratum 2B</u> : recurrent intracranial malignant gliomas - using EIACD | Study completed | To develop exploratory data concerning surrogate endpoints of therapeutic activity, using physiological neuroimaging studies and correlative biological studies |
| PBTC-007 | A Phase I/II Trial of ZD1839 (Iressa™) and Radiation in Pediatric Patients Newly Diagnosed with Brain Stem Tumors or Incompletely Resected Supratentorial Malignant Gliomas with Phase II Limited to Brain Stem Tumors | <u>Stratum 1</u> : Newly diagnosed intrinsic brain stem glioma or incompletely resected supratentorial malignant gliomas not receiving enzyme-inducing anti-convulsant drugs <u>Stratum 2</u> : Incompletely resected supratentorial malignant gliomas receiving enzyme-inducing anti-convulsant drugs | Study completed | To compare hemodynamic MR parameters to metabolic FDG-PET scanning and correlate both with clinical response or progression in this population |
| PBTC-009 | A Phase I Trial of GLIADEL® and O ⁶ -Benzylguanine in Pediatric Patients with Recurrent Malignant Gliomas | None | Study completed | MRI / MRS / MR perfusion & diffusion for assessment of response and toxicity |

*If neutropenia is the dose limiting toxicity, additional patients will be accrued allowing the use of G-CSF to establish whether higher doses of temozolomide can be administered with this form of hematological support (Stratum 1b &/or 2b)

Table 6: PBTC Protocols [010 – 016]

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|-----------------|--|--|-----------------|---|
| PBTC-010 | A Phase II Study of Oxaliplatin in Children with Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumors and Atypical Teratoid Rhabdoid Tumors after Failure of Initial Therapy | <u>Stratum IA</u> : medulloblastoma patients with measurable disease <u>Stratum IB</u> : medulloblastoma patients with only positive CSF cytology or with linear leptomeningeal disease; <u>Stratum II</u> : will include patients with supratentorial primitive neuroectodermal tumor (S-PNET) including pineoblastomas, and ependymoblastomas; <u>Stratum III</u> : patients with atypical teratoid rhabdoid tumors (ATRT). | Study completed | No correlative objective. MRI for response only with central review. |
| PBTC-011 | A Phase I/II Trial of Intracerebral IL13-PE38QQR Infusions in Pediatric Patients with Recurrent Malignant Glioma | No strata in Phase I | Study completed | No correlative objective. MRI for response only with central review. |
| PBTC-012 | A Phase I Study of Cilengitide (EMD 121974) in Children with Refractory Brain Tumors | No strata | Study completed | MRI, MRS, MR perfusion, PET for tumor blood flow, metabolic activity and volume. |
| PBTC-013 | A Phase I/II Study of a Recombinant Chimeric Protein Composed of Transforming Growth Factor (TGF)- α and a Mutated Pseudomonas Exotoxin Termed PE38 (TP-38) in Pediatric Patients with Recurrent or Progressive Supratentorial High Grade Gliomas | No strata | Study completed | No correlative objective. MRI for response only with central review. |
| PBTC-014 | A Phase I/II Trial of R115777 and Radiation in Pediatric Patients Newly Diagnosed Non-disseminated Intrinsic Diffuse Brainstem Gliomas | No strata | Study completed | To characterize radiographic changes using MRI, MRS, perfusion and diffusion imaging and PET scans. |
| PBTC-015 | A Phase II Trial of O6-Benzylguanine and Temozolomide in Pediatric Patients with Recurrent or Progressive High-Grade Gliomas and Recurrent or Progressive Brainstem Tumors | <u>Stratification</u> Patients will be stratified according to tumor type: <u>Stratum A</u> Recurrent or progressive high grade gliomas <u>Stratum B</u> Recurrent or progressive brain stem tumors | Study completed | To evaluate changes in MR spectroscopic patterns, MR diffusion and MR perfusion in children with refractory or recurrent high-grade gliomas or brainstem gliomas who are treated with the combination of O6-BG and TMZ. |
| PBTC-016 | A Phase I, Molecular Biology and Phase II Study of Lapatinib (GW572016) in Pediatric Patients with Recurrent or Refractory Medulloblastoma, Malignant Glioma or Ependymoma | Phase I: <u>Stratum 1</u> : those who are not receiving steroids; <u>Stratum 2</u> : those who are receiving steroids; | Study completed | To characterize radiographic changes using MRI, MRS, perfusion and diffusion imaging and PET scans. |

Table 6: PBTC Protocols [017 – 021]

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|-----------------|--|---|-----------------|--|
| PBTC-017 | A Phase I Study of CLORETAZINE™ (VNP40101M) in Children with Recurrent, Progressive or Refractory Primary Brain Tumors | <u>Stratum 1</u> : no prior XRT or focal XRT only and/or < 2 prior myelosuppressive chemotherapy regimens; <u>Stratum 2</u> : prior craniospinal XRT, high-dose chemotherapy, and/or > 2 prior myelosuppressive chemotherapy regimens | Study completed | No correlative component. Central review for response based on the first MRI scan obtained after 2 courses of chemotherapy. |
| PBTC-018 | A Phase I Trial of CC-5013 in Pediatric Patients with Recurrent or Refractory Primary CNS Tumors | No strata | Study completed | 1. To evaluate changes in circulating endothelial cells, circulating endothelial cell precursors, and angiogenic modulators and correlate these changes with changes in MR perfusion and clinical outcome. 2. To evaluate changes in MR spectroscopy, MR perfusion and diffusion during treatment. |
| PBTC-019 | A Phase I Pharmacokinetic Optimal Dosing Study of Intrathecal Topotecan for Children with Neoplastic Meningitis | No strata | Study completed | MRI central review for treatment effects and response at study completion. |
| PBTC-020 | A Phase I Clinical Trial of AZD2171 in Children with Recurrent or Progressive Central Nervous System (CNS) Tumors | <u>Stratum 1</u> : Those who are not receiving enzyme inducing anticonvulsant drugs (EIACD) <u>Stratum 2</u> : Stratum 1: Those who are receiving enzyme inducing anticonvulsant drugs (EIACD) | Study completed | 1. To explore correlations in changes in CECs, CEPs and angiogenic modulators with changes in MR perfusion. 2. To obtain preliminary evidence of biologic activity of AZD2171 by evaluating alterations in tissue perfusion, tumor blood flow and metabolic activity using MR perfusion and diffusion imaging, MRS as well as PET analysis and correlating these findings with changes in tumor size by standard MRI. 3. To continue the PBTC investigation of imaging assessments of antiangiogenesis effects by combining data from this trial with other PBTC trials of similar agents. |
| PBTC-021 | A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas | No strata | Study completed | To characterize radiographic changes in non-disseminated, newly diagnosed intrinsic brainstem gliomas and high-grade gliomas treated with radiation and capecitabine using MRI, MRS, perfusion and diffusion imaging and PET scans |

Table 6: PBTC Protocols [022 – 025]

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|-----------------|--|--|-----------------|--|
| PBTC-022 | Phase II study of Bevacizumab plus Irinotecan (Camptosar™) in Children with Recurrent, Progressive, or Refractory Malignant Gliomas, Diffuse/Intrinsic Brain Stem Gliomas, Medulloblastomas, Ependymomas and Low Grade Gliomas | <p><u>Stratum A:</u> Recurrent, progressive or refractory high-grade gliomas</p> <p><u>Stratum B:</u> Recurrent, progressive or refractory Intrinsic brain stem tumors</p> <p><u>Stratum C:</u> Recurrent or progressive Medulloblastomas</p> <p><u>Stratum D:</u> Recurrent or progressive Ependymomas</p> <p><u>Stratum E:</u> Recurrent low grade gliomas</p> | Study completed | <p>1. To document changes in MR perfusion and diffusion scans obtained within 24-48 hours following the 2nd dose of Bevacizumab as compared to baseline and correlate with response.</p> <p>2. To correlate functional changes in tumor with responses to treatment with Bevacizumab + irinotecan using MR perfusion/diffusion imaging, and Fluoro-deoxyglucose (FDG) positron emission tomography (PET).</p> <p>3. To estimate vascular endothelial growth factor receptor-2 (VEGF-R2) expression in peripheral blood mononuclear cells (PBMC) prior to treatment and its down-regulation following two doses of single-agent Bevacizumab and correlate this finding with permeability changes in the tumor on MR perfusion imaging obtained 24-48 hours following the 2nd dose Bevacizumab</p> |
| PBTC-023 | Phase I and Pharmacokinetic Study of Enzastaurin (LY317615) in Children and Adolescents with Refractory Primary CNS Tumors | No strata | Study completed | <p>To explore changes in correlative magnetic resonance imaging in children receiving enzastaurin. Specifically to evaluate changes in MR perfusion and diffusion scans obtained within 15 ± 2 days after initiation of enzastaurin therapy as compared to baseline and to correlate these changes with clinical outcome, as applicable.</p> <p>1. Results of imaging studies will be combined across similar PBTC protocols to increase the power for detecting correlations among scans and with outcome.</p> |
| PBTC-024 | A Phase I Study of MK-0752 in Pediatric Patients with Recurrent or Refractory CNS Malignancies | No strata | Study completed | <p>To explore changes in correlative magnetic resonance imaging in children receiving MK-0752. Volumetric MR imaging findings may be combined across similar PBTC protocols to increase the power for detecting correlations among scans and associations with outcome.</p> |
| PBTC-025 | A Phase I Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic Based Dose for GDC-0449 | No strata | Study completed | Central review of MR knee, standard MR brain and spine. |

Table 6: PBTC Protocols [025B – 033]

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|------------------|---|---|--|---|
| PBTC-025B | A Phase I Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic Based Dose for GDC-0449 | No strata | Open to accrual | Central review of neuro-imaging studies by neuro-radiologists will be conducted to confirm response only in patients reported by the treating site to have experienced an objective response. MRI of the Brain and spine with and without contrast (brain) and post contrast (spine) will be performed. |
| PBTC-026 | A Feasibility Study of SAHA combined with Isotretinoin and Chemotherapy in Infants with Embryonal Tumors of the Central Nervous System | No strata | Open to accrual | To estimate the preliminary response rate of this approach in patients with measurable residual disease (primary site and/or metastatic sites). Central review of standard MR brain and spine. |
| PBTC-027 | A Phase I Study of ABT-888, an Oral Inhibitor of Poly(ADP-ribose) Polymerase and Temozolomide in Children with Recurrent/Refractory CNS Tumors | No strata | Study completed | No correlative objective. MR for response only. |
| PBTC-029 | Phase I and Pharmacokinetic Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | No strata | Study completed | Central review of MR imaging studies. To assess diffusion imaging contributions to tumor behavior (type, grade) and response to therapy. |
| PBTC-029B | A Phase 1 and Phase II Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | <p><u>Stratum 1:</u> Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma with pre-trial tumor material available and with a BRAF aberration excluding patients with optic pathway glioma.</p> <p><u>Stratum 2:</u> Patients with non NF-1 associated progressive, recurrent or refractory pilocytic astrocytoma with pre-trial tumor material available and without BRAF aberration excluding patients with optic pathway glioma.</p> <p><u>Stratum 3:</u> Patients with NF-1 associated progressive, recurrent or refractory low grade glioma (WHO I or II), with or without tissue</p> <p><u>Stratum 4:</u> Patients with non-NF1 associated progressive, recurrent or refractory optic pathway glioma (OPG) with or without tissue available for BRAF evaluation.</p> <p><u>Stratum 5:</u> Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than pilocytic astrocytoma or optic pathway</p> | Strata 2, 5 and 6 open; rest closed to accrual | To describe MRI characteristics of the tumors before and after treatment to determine if there is an early diffusion indicator of response. |

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|--------------------------------|--|--|-------------------|---|
| | | glioma) with a BRAF aberration. <u>Stratum 6:</u> Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than OPG) with tissue available for BRAF analysis who cannot be classified into Stratum 1, 2 or 5 due to inadequate tissue quality | | |
| PBTC-029C - Retreatment | A Phase 1 and Phase II Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | No strata | Closed to accrual | To describe MRI characteristics of the tumors before and after treatment to determine if there is an early diffusion indicator of response. |
| PBTC-030 | A Phase II Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas | No strata | Study completed | To describe and explore changes in diffusion tensor imaging variables in brainstem gliomas in response to therapy and prior to progression. |
| PBTC-031 | Phase I and Pharmacokinetic Trial of PTC299 in Pediatric Patients with Refractory or Recurrent CNS Tumors | No strata | Study completed | To obtain preliminary evidence of biologic activity of PTC299 by using MR diffusion to assess tumor cellularity. |
| PBTC-032 | A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Children with Recurrent or Refractory Medulloblastoma | <u>Strata A:</u> Patients without evidence of activation of Hedgehog signaling pathway <u>Strata B:</u> Patients with evidence of activation of Hedgehog signaling pathway | Study completed | MR of the knee: To assess for side effects of this drug on growth cartilage MR of brain/spine: Central review of MR scans of brain and spine will be performed to confirm sustained responses and other clinical events as may be needed. |
| PBTC-033 | A Phase I/II Study of ABT-888, an Oral Poly (ADP-ribose) Polymerase Inhibitor, and Concurrent Radiation Therapy, Followed by ABT-888 and Temozolomide, in Children with Newly Diagnosed Diffuse Pontine Gliomas (DIPG) | No strata | Study completed | To explore the quantitative MR measures of relative cerebral blood volume (rCBV), vascular permeability (K _{trans} , v _p , and v _e values), and apparent diffusion coefficient (ADC) within the first six months of initiating protocol treatment to correlate with disease outcome and determine whether such metrics differentiate patients with pseudoprogression from those with true early progressive disease. |

Table 6: PBTC Protocols [036-048]

| Protocol | Title | Strata | Status | Neuroimaging Objective/Test |
|-----------------|---|--|-----------------|--|
| PBTC-036 | A Molecular Biology and Phase II Study of Imetelstat (GRN163L) in Children with Recurrent High-Grade Glioma, Ependymoma, Medulloblastoma/Primitive Neuroectodermal Tumor and Diffuse Intrinsic Pontine Glioma | No strata | Study completed | To assess changes in tumor size, enhancement, and diffusion characteristics. |
| PBTC-037 | A phase I study of intratumoral/peritumoral herpes simplex virus-1 mutant HSV1716 in patients with refractory or recurrent high grade gliomas (HGG) | No strata | Study completed | <ol style="list-style-type: none"> 1. To evaluate changes in tumor enhancement, quantitative MR measures of tumor 1.1.4perfusion (relative cerebral blood volume (rCBV), ktrans, Vp and Ve values and apparent diffusion coefficient (ADC) in response to HSV1716 injection 2. To evaluate changes in FDG-PET uptake in response to HSV1716 injection. 3. To evaluate changes in tumor choline values using MR spectroscopy in response to HSV1716 injection and further delineate from progressive disease versus pseudo-progression post therapy. |
| PBTC-039 | A Phase II study of Peginterferon alfa-2b (PEGIntron) for pediatric patients with unresectable or recurrent craniopharyngioma | <p><u>Stratum 1:</u> Patients with progressive unresectable or recurrent craniopharyngiomas treated with surgery alone who have not received radiation therapy. Patients with unresectable craniopharyngiomas (i.e., residual measurable disease following surgical resection) will be enrolled at the time of progression</p> <p><u>Stratum 2:</u> Patients with progressive or recurrent craniopharyngiomas following radiation therapy.</p> | Study completed | To compare the protocol specific disease assessment criteria to MacDonald criteria during the first year of treatment in stratum I and at the time of objective response and progressive disease in both strata. |
| PBTC-041 | A Phase I Trial of p28 (NSC745104), a Non-HDM2 mediated peptide inhibitor of p53 ubiquitination in pediatric patients with recurrent or progressive CNS tumors | No strata | Study completed | No correlative objective. MR for response only. |
| PBTC-042 | PBTC-042 Phase I study of CDK 4-6 inhibitor PD-0332991 in children with recurrent, progressive or refractory central nervous system tumors | <p><u>Stratum A:</u> DIPGs</p> <p><u>Stratum B:</u> non-brainstem HGGs</p> | Study completed | No correlative objective MR for response only |

| | | | | |
|-----------------|--|--|-----------------|--|
| PBTC-043 | A Phase I Trial of Pomalidomide for children with recurrent, progressive or refractory CNS tumors | <p><u>Stratum 1:</u> Patients on or off steroids</p> <p><u>Stratum 2:</u> Patients on steroid, <12 Years Old</p> <p><u>Stratum 3:</u> Patients off steroid, <12 Years Old</p> <p><u>Stratum 4:</u> Patients on steroid, >=12 Years Old</p> <p><u>Stratum 5:</u> Patients off steroid, >=12 Years Old</p> | Study completed | No correlative response MR for response only |
| PBTC-045 | A Safety and Preliminary Efficacy trial of MK-3475 (pembrolizumab; anti-PD-1) in Children with recurrent, progressive or refractory high-grade gliomas (HGG) and DIPGs. | <p><u>Stratum A:</u> patients with progressive, recurrent or refractory DIPGs</p> <p><u>Stratum B:</u> patients with progressive, recurrent or refractory non-brainstem HGGs.</p> | Open | <p>1. To examine the ability of quantitative MR spectroscopy and diffusion/weighted imaging/ADC mapping to provide early assessment of tumor behavior and specifically distinguish pseudoprogression from true progression</p> <p>2. To explore the use of serial MR permeability (DCE) and MR perfusion (DSC) to determine if elevated rCBV and ktrans can distinguish pseudoprogression from true progression in tumors treated on this protocol</p> |
| PBTC-047 | A Phase I Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma | <u>No Strata</u> | Open | No correlative response. MR for response only Will analyze diffusion and standard MR sequences |
| PBTC-048 | Feasibility Trial of Optune for Children with Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma | <u>No Strata</u> | Open | To explore the association of apparent diffusion coefficient (ADC) values within the tumor and correlate with response to Optune treatment and EFS. |
| PBTC-050 | A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors | <u>No Strata</u> | Open | No correlative response. MR for response only |
| PBTC-051 | Phase I Study to Evaluate the Safety and Tolerability of the CD40 Agonistic Monoclonal Antibody APX005M in Pediatric Subjects with Recurrent/Refractory Brain Tumors and Newly Diagnosed Brain Stem Glioma | <u>No Strata</u> | Open | No correlative response. MR for response only. |
| PBTC-053 | A Pediatric Brain Tumor Consortium Phase I/ II and Surgical Study of CX-4945 in Patients with Recurrent SHH Medulloblastoma | <u>No Strata</u> | Open | No correlative response. MR for response only. |

| | | | | |
|-----------------|---|---|------|---|
| PBTC-055 | Phase I/II trial of Dabrafenib, Trametinib, and Hydroxychloroquine (HCQ) for BRAF V600E-mutant or Trametinib and HCQ for BRAF fusion/duplication positive or NF1-associated recurrent or progressive gliomas in children and young adults | <u>Stratum 1: BRAF V600E LGG or HGG</u> <u>Stratum 2: BRAF fusion/duplication or NF1- associated LGG</u> <u>Stratum 3: LGGs with V600E</u> <u>Stratum 4: HGGs with V600E</u> | Open | Standard MR imaging in phase I and II and ADC histogram analysis in phase II study |
| PBTC-056 | A Phase 1 Study of the ADAM-10 inhibitor, INCB007839 in Children with Recurrent/Progressive High-Grade Gliomas to Target Microenvironmental Neurologlin-3 | <u>No Strata</u> | Open | Standard MR imaging. |
| PBTC-058 | Phase 2 Study of Intraventricular Omburtamab-based Radioimmunotherapy for Pediatric Patients with Recurrent Medulloblastoma and Ependymoma | <u>Stratum 1: Recurrent medulloblastoma</u> <u>Stratum 2: Recurrent ependymoma</u> | Open | Standard MR imaging and PET imaging |
| PBTC-059 | Phase 1 Trial of Autologous HER2-specific CAR T cells in Pediatric Patients with Refractory or Recurrent Ependymoma | <u>Recurrent or refractory ependymoma</u> | Open | 1. To examine the ability of quantitative MR diffusion DWI/ADC mapping to provide early assessment of tumor behavior and specifically distinguish pseudoprogression from tumor progression. 2. To explore the use of MR permeability and MR perfusion to distinguish pseudoprogression from tumor progression. |
| PBTC-060 | A Pilot Study of Safety, Tolerability, and Immunological Effects of SurVaxM in Pediatric Patients with Progressive or Relapsed Medulloblastoma, High Grade Glioma, Ependymoma and Newly Diagnosed Diffuse Intrinsic Pontine Glioma | <u>Progressive or relapsed medulloblastoma, high grade gliom, ependymoma and newly diagnosed DIPG.</u> | Open | 1. To examine the ability of quantitative MR diffusion DWI/ADC mapping to provide early assessment of tumor behavior and specifically distinguish pseudoprogression from tumor progression. 2. To explore the use of MR permeability and MR perfusion to distinguish pseudoprogression from tumor progression. |

Table 7: PBTC Protocols [001 – 013]

| Protocol | Trial | MR Brain | MR Diffusion | MR Perfusion | MR Spectroscopy | Cisternogram | MR Spine | Bone Scan | PET | CT |
|----------|--|----------|--------------|--------------|-----------------|--------------|----------|-----------|-----|----|
| PBTC-001 | A Pilot Study of Systemic and Intrathecal Chemotherapy followed by Conformal Radiation for infants with Embryonal Intracranial Central Nervous System Tumors | + | | | | + | + | + | | |
| PBTC-002 | A Phase I Study of SU5416 in Pediatric Patients With Recurrent or Progressive Poor Prognosis Brain Tumors | + | + | + | + | | | | + | |
| PBTC-003 | A Phase I Trial of Escalating Oral Doses of SCH 66336 in Pediatric Patients with Refractory or Recurrent Brain Tumors | + | | | | | + | | | |
| PBTC-004 | A Phase I Study of Intrathecal Spartaject™-Busulfan in Children with Neoplastic Meningitis | + | | | | | + | | | |
| PBTC-005 | A Phase I Trial of Temozolomide and O ⁶ -Benzylguanine in Pediatric Patients with Recurrent Brain Tumors | + | | | | | + | | | |
| PBTC-006 | A Phase I/II Trial of STI571 in Children with Newly Diagnosed Poor Prognosis Brainstem Gliomas and Recurrent Intracranial Malignant Gliomas | + | + | + | + | | + | | + | |
| PBTC-007 | A Phase I/II Trial of ZD1839 (Iressa™) and Radiation in Pediatric Patients Newly Diagnosed with Brain Stem Tumors or Incompletely Resected Supratentorial Malignant Gliomas with Phase II limited to Brain Stem Tumors | + | + | + | | | | | + | |
| PBTC-009 | A Phase I Trial of GLIADEL® and O ⁶ -Benzylguanine in Pediatric Patients with Recurrent Malignant Gliomas | + | + | + | + | | | | | |
| PBTC-010 | A Phase II Study of Oxaliplatin in Children with Recurrent or Refractory Medulloblastoma, Supratentorial Primitive Neuroectodermal Tumors and Atypical Teratoid Rhabdoid Tumors | + | | | | | + | | | |
| PBTC-011 | A Phase I/II Trial of Intracerebral IL13-PE38QQR Infusions in Pediatric Patients with Recurrent Malignant Glioma | + | | | | | | | | + |
| PBTC-012 | A Phase I Study of Cilengitide (EMD 121974) in Children with Refractory Brain Tumors | + | | + | + | | + | | + | |
| PBTC-013 | A Phase I/II Study of a Recombinant Chimeric Protein Composed of Transforming Growth Factor (TGF)- α and a Mutated Form of the Pseudomonas Exotoxin Termed PE38 (TP-38) in Pediatric Patients with Recurrent or Progressive Supratentorial High Grade Gliomas | + | | | | | | | | + |

Table 7: PBTC Protocols [014-022]

| Protocol | Trial | MR Brain | MR Diffusion | MR Perfusion | MR Spectroscopy | Cister-nogram | MR Spine | Bone Scan | PET | CT |
|-----------------|--|----------|--------------|---------------------------------|-----------------|---------------|----------|-----------|-----|----|
| PBTC-014 | A Phase I/II Trial of R115777 and Radiation in Pediatric Patients Newly Diagnosed Non-disseminated Intrinsic Diffuse Brainstem Gliomas | + | + | + | | | + | | + | |
| PBTC-015 | A Phase II Trial of 06-Benzylguanine and Temozolomide in Pediatric Patients with Recurrent or Progressive High-Grad Gliomas and Recurrent / Progressive Brainstem Tumors | + | | + | + | | | | + | |
| PBTC-016 | A Phase I, Molecular Biology and Phase II Study of Lapatinib (GW572016) in Pediatric Patients with Recurrent or Refractory Medulloblastoma, Malignant Glioma or Ependymoma | + | + | + | | | + | | + | |
| PBTC-017 | A Phase I Study of CLORETAZINE™ (VNP40101M) in Children with Recurrent, Progressive or Refractory Primary Brain Tumors | + | | | | | + | | | |
| PBTC-018 | A Phase I Trial of CC-5013 in Pediatric Patients with Recurrent or Refractory Primary CNS Tumors | + | + | + | | | + | | + | |
| PBTC-019 | A Phase I Pharmacokinetic Optimal Dosing Study of Intrathecal Topotecan for Children with Neoplastic Meningitis | + | | | | | + | | | |
| PBTC-020 | A Phase 1 Clinical Trial of AZD2171 in children with Recurrent or Progressive Central Nervous System (CNS) Tumors | + | + | T1 permeability followed by T2* | | | + | | + | |
| PBTC-021 | A Phase I Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas and High Grade Gliomas | + | + | + | | | + | | + | |
| PBTC-022 | Phase II study of Bevacizumab plus Irinotecan (Camptosar™) in Children with Recurrent, Progressive, or Refractory Malignant Gliomas, Diffuse/Intrinsic Brain Stem Gliomas, Medulloblastomas, Ependymomas and Low Grade Gliomas | + | + | T1 permeability followed by T2* | | | + | | + | |

Table 7: PBTC Protocols [023-032]

| Protocol | Trial | MR Brain | MR Diffusion | MR Perfusion | MR Spectroscopy | Cister-nogram | MR Spine | Bone Scan | PET | CT |
|--------------------------------|---|----------|--------------|---------------------------------|-----------------|---------------|----------|-----------|-----|----|
| PBTC-023 | A Phase I and Pharmacokinetic Study of Enzastaurin (LY317615) in Children and Adolescents with Refractory Primary CNS Tumors | + | + | T1 permeability followed by T2* | | | + | | | |
| PBTC-024 | A Phase I Study of MK-0752 in Pediatric Patients with Recurrent or Refractory CNS Malignancies | + | | | | | + | | | |
| PBTC-025 | A Phase I Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic Based Dose for GDC-0449** | + | | | | | + | | | |
| PBTC-025B | A Phase I Pharmacokinetic and Safety Study in Children with Recurrent or Refractory Medulloblastoma to Identify a Pharmacokinetic Based Dose for GDC-0449 | + | | | | | + | | | |
| PBTC-026 | A Feasibility Study of SAHA combined with Isotretinoin and Chemotherapy in Infants with Embryonal Tumors of the Central Nervous System | + | | | | | + | | | |
| PBTC-027 | A Phase I Study of ABT-888, an Oral Inhibitor of Poly(ADP-ribose) Polymerase and Temozolomide in Children with Recurrent/Refractory CNS Tumors | + | | | | | + | | | |
| PBTC-029 | A Phase I and Pharmacokinetic Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | + | + | | | | + | | | |
| PBTC-029B | A Phase 1 and Phase II Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | + | + | | | | + | | | |
| PBTC-029C - Retreatment | A Phase 1 and Phase II Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma | + | + | | | | + | | | |
| PBTC-030 | A Phase II Trial of Capecitabine Rapidly Disintegrating Tablets and Concomitant Radiation Therapy in Children with Newly Diagnosed Brainstem Gliomas* | + | + | | | | | | | |
| PBTC-031 | A Phase I and Pharmacokinetic Trial of PTC299 in Pediatric Patients with Refractory or Recurrent CNS Tumors | + | + | | | | + | | | |
| PBTC-032 | A Phase II Clinical Trial Evaluating the Efficacy and Safety of GDC-0449 in Children with Recurrent or Refractory Medulloblastoma | + | | | | | + | | | |

Table 7: PBTC Protocols [033-048]

| Protocol | Trial | MR Brain | MR Diffusion | MR Perfusion | MR Spectroscopy | Cisternogram | MR Spine | Bone Scan | PET | CT |
|-----------------|--|----------|--------------|--|-----------------|--------------|----------|-----------|-----|----|
| PBTC-033 | A Phase I/II Study of ABT-888, an Oral Poly (ADP-ribose) Polymerase Inhibitor, and Concurrent Radiation Therapy, Followed by ABT-888 and Temozolomide, in Children with Newly Diagnosed Diffuse Pontine Gliomas (DIPG) | + | + | T1 permeability followed by T2* | | | + | | | |
| PBTC-036 | A Molecular Biology and Phase II Study of Imetelstat (GRN163L) in Children with Recurrent High-Grade Glioma, Ependymoma, Medulloblastoma/Primitive Neuroectodermal Tumor and Diffuse Intrinsic Pontine Glioma | + | + | | | | + | | | |
| PBTC-037 | A phase I study of intratumoral/peritumoral herpes simplex virus-1 mutant HSV1716 in patients with refractory or recurrent high grade gliomas (HGG) | + | + | + | + | | | | + | |
| PBTC-039 | A Phase II study of Peginterferon alfa-2b (PEGIntron) for pediatric patients with unresectable or recurrent craniopharyngioma | + | | | | | | | | |
| PBTC-041 | A Phase I Trial of p28 (NSC745104), a Non-HDM2 mediated peptide inhibitor of p53 ubiquitination in pediatric patients with recurrent or progressive CNS tumors | + | + | | | | + | | | |
| PBTC-042 | Phase I study of CDK 4-6 inhibitor PD-0332991 in children with recurrent, progressive or refractory central nervous system tumors. | + | | | | | + | | | |
| PBTC-043 | A Phase I Trial of Pomalidomide for children with recurrent, progressive or refractory CNS tumors | + | + | | | | + | | | |
| PBTC-045 | A Safety and Preliminary Efficacy trial of MK-3475 (pembrolizumab; anti-PD-1) in Children with recurrent, progressive or refractory high-grade gliomas (HGG) and DIPGs | + | + | + | + | | + | | | |
| PBTC-047 | Phase 1 Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma | + | + | | | | | | | |
| PBTC-048 | Feasibility Trial of Optune for Children with Recurrent or Progressive Supratentorial High-Grade Glioma and Ependymoma | + | + | | | | | | | |

Table 7: PBTC Protocols [049-060]

| Protocol | Trial | MR Brain | MR Diffusion | MR Perfusion | MR Spectroscopy | Cister-nogram | MR Spine | Bone Scan | PET | CT |
|-----------------|---|----------|--------------|--------------|-----------------|---------------|----------|-----------|-----|----|
| PBTC-049 | A Phase I study of Savolitinib in Recurrent, Progressive, or Refractory Medulloblastoma, High Grade Glioma, Diffuse Intrinsic Pontine Glioma, and CNS tumors harboring MET aberrations | + | + | | | | + | | | |
| PBTC-050 | A Phase I and Surgical Study of Ribociclib and Everolimus (RAD001) in Children with Recurrent or Refractory Malignant Brain Tumors | + | | | | | + | | | |
| PBTC-051 | Phase I Study to Evaluate the Safety and Tolerability of the CD40 Agonistic Monoclonal Antibody APX005M in Pediatric Subjects with Recurrent/Refractory Brain Tumors and Newly Diagnosed Brain Stem Glioma | + | | | | | + | | | |
| PBTC-053 | A Pediatric Brain Tumor Consortium Phase I/ II and Surgical Study of CX-4945 in Patients with Recurrent SHH Medulloblastoma | + | | | | | + | | | |
| PBTC-055 | Phase I/II trial of Dabrafenib, Trametinib, and Hydroxychloroquine (HCQ) for BRAF V600E-mutant or Trametinib and HCQ for BRAF fusion/duplication positive or NF1-associated recurrent or progressive gliomas in children and young adults | + | + | | | | + | | | |
| PBTC-056 | A Phase I study of the ADAM-01 inhibitor, INCB00789 in children with recurrent/progressive high-grade gliomas to target microenvironmental neuroligin-3 | + | + | | | | + | | | |
| PBTC-058 | Phase 2 Study of Intraventricular Omburtamab-based Radioimmunotherapy for Pediatric Patients with Recurrent Medulloblastoma and Ependymoma | + | + | | | | + | | + | |
| PBTC-059 | Phase 1 Trial of Autologous HER2-specific CAR T cells in Pediatric Patients with Refractory or Recurrent Ependymoma | + | + | + | | | + | | | |
| PBTC-060 | A Pilot Study of Safety, Tolerability, and Immunological Effects of SurVaxM in Pediatric Patients with Progressive or Relapsed Medulloblastoma, High Grade Glioma, Ependymoma and Newly Diagnosed Diffuse Intrinsic Pontine Glioma | + | + | + | | | + | | | |

* DTI

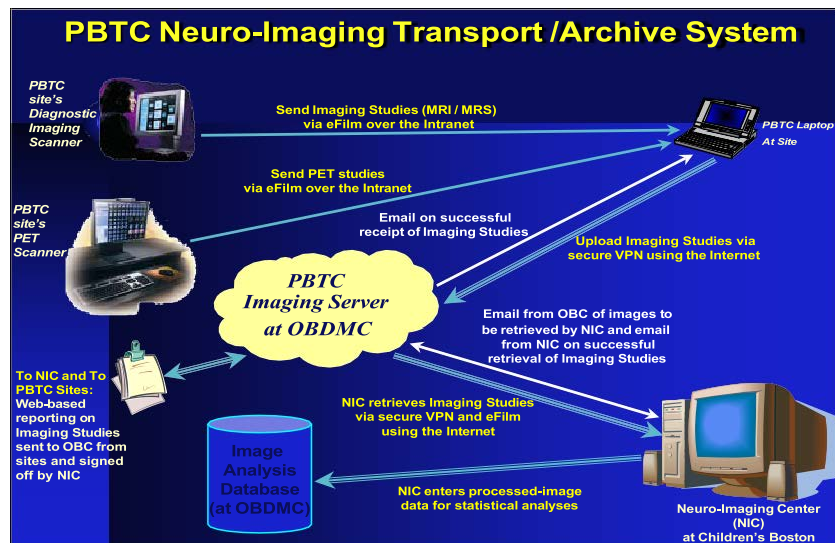
** MR of knee required

IV. Procedures for Transfer of Imaging Studies

A. MR and PET Image Transfer

The PBTC neuroimaging studies are sent across a secure tunnel from the participating sites to the OBDMC at St. Jude's Hospital and then to the Neuroimaging Center at Boston Children's Hospital. Software in the Operations Office is used to replace the patient identifiers with PBTC codes. It is important that the patient identifiers are stripped and replaced with PBTC codes at the central Operations office, as it not only maintains patient confidentiality before the studies are sent to the Neuroimaging Center of the PBTC; it also provides us with the accountability to match correct patient data with the imaging studies. Throughout the transmission process from the PBTC sites to the Operations Office of PBTC and then onwards to the Neuroimaging Center of PBTC, the OBDMC is employing a Virtual Private Network (VPN) solution. The data are highly encrypted and encapsulated in this secure tunnel. This VPN solution has been used to transmit the PBTC database that has all patient information from the PBTC sites to the Operations Office. The OBDMC staff is fully aware of the HIPAA regulations and has made sure that the Operations Office conforms to the HIPAA regulations in their work for the Consortium.

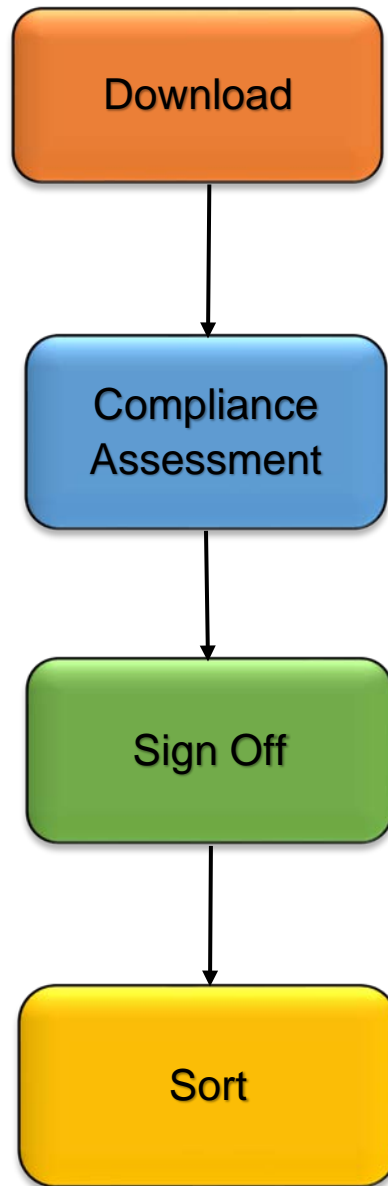
MR and PET studies are downloaded from the OBDMC after email notification to the NIC. This is followed by a compliance assessment, followed by the completion of a web-based form to indicate that download is completed and a sign-off procedure on each designated series of the exam for presence and analyzability. The studies are sorted into the appropriate protocol folder on the PBTC NIC server.

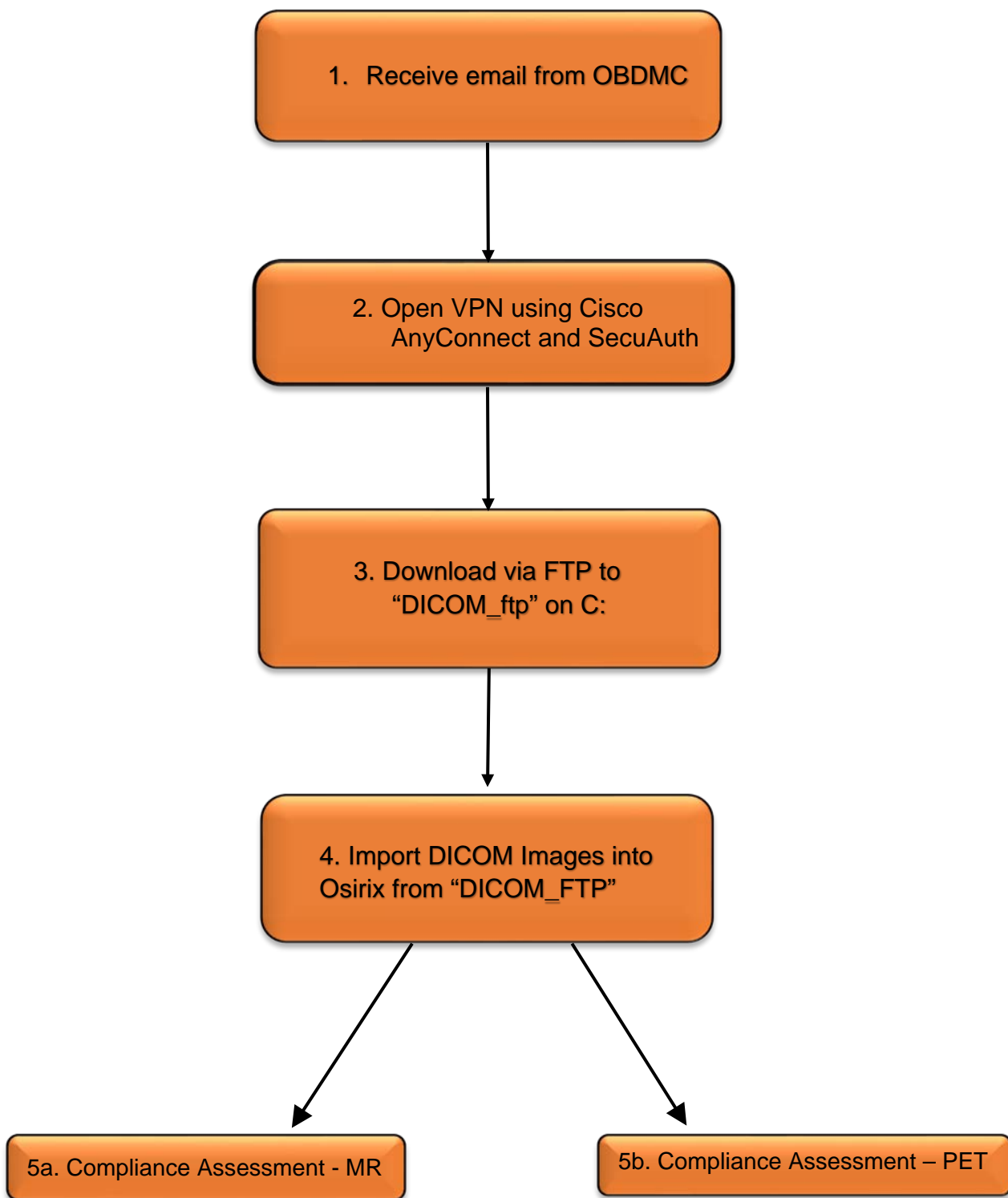


B. PBTC NIC Operations Overview for MR & PET Image Manipulation

The process of downloading, compliance assessment, sign-off and sorting is described as follows in stepwise outline form.

PBTC NIC OPERATIONS OVERVIEW FOR MR AND PET IMAGE MANIPULATION





Download

1 - Receive email from the OBDMC

- Email will contain where studies are located on the FTP server
 - Download date specific folder name
 - Special notes and/or circumstances

2 - VPN Client Access

- All download procedures require an active VPN connection between St. Jude's OBDMC and Boston Children's Hospital, NIC.
- Open *Cisco AnyConnect Secure Mobility Client*
 1. Pop-up dialog box will appear. Click "Connect"
A second dialog box will open requesting: "Please enter your St. Jude User ID and Password"
Enter Credentials
This will trigger a two-factor security protocol.

2. Successful input of two-factor security credentials will result in an additional pop-up dialog box. "Welcome to St Jude's Vendor Client VPN."
Click "Accept" button.

3 - Download via FTP

- Open *Filezilla Client*
- Connect to "remote browser"
 1. Remote server IP = **[Insert Here]**
 2. Log-in set to **[Insert Here]**
- The OBDMC will supply the folder name of the download in an email.
- Copy files from OBDMC Server to NIC Workstation folder "DICOM_FTP"
[C:\PBTC_Download\DicomFTP]

4 – Import DICOM Images into Osirix from “DICOM FTP”

- Open Osirix
- Open File Tab
 - Import
 - Import Dicom Select folder with the date of the download provided by the OBDMC
 - Open
 - Pop up dialog box:
 - OsiriX Database
- Should I copy these files in OsiriX Database folder, or only copy links to these files?
 - Click “Copy Files”

5a - Compliance Assessment Preparation - MR

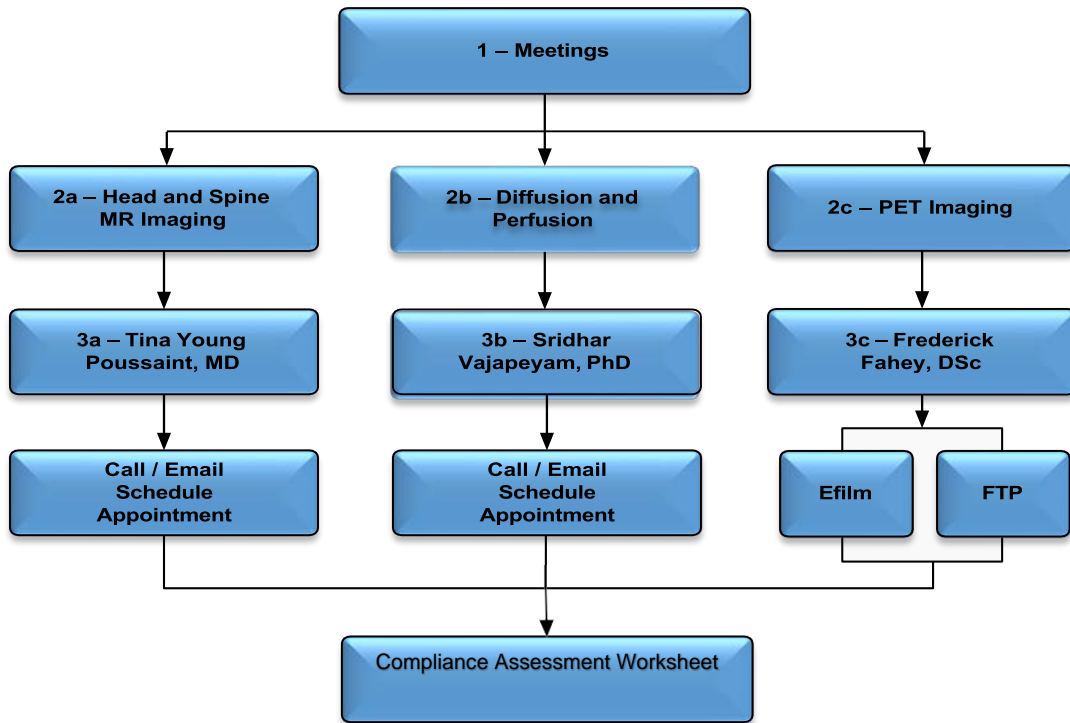
- Open Excel
- File open; Z:\Public\R40300\NIC Download Resources\PBTC Download-Signoff_A_A]
 - 1. File should open to “download raw MR” tab, if not switch to that tab.
- Open “Internet Explorer.”
- Open “PBTC Web Report”
 - http://10.38.48.102/PBTC_WebReport/I8M1A3G9E7D1U6K2E9/default.html
- Log-in
 - 1. OBDMC has provided personal usernames and passwords.
- Mouse-click the “click here” link attributed to “To sign-off downloaded MRI/MRD/MRP/MRS/CT studies on OBDMC server, please click here.”
- A new browser window will open.
- Highlight the MR spreadsheet that appears and copy.
 - 1. Important: Be sure to omit the header rows when copying MR data. Header rows are provided in the Excel file.
- Return to Excel
- Paste MR data onto the “download raw MR” tab.
 - 1. Be sure that data is pasted in the first free cell of the first column. [A4]
 - 2. The drop-down menus the data may take a few minutes to appear.
- Once loaded, copy the MR data from “Download Raw MR” tab. (This will remove the developer open dialog boxes from the spreadsheet, without having to do so individually for every row and column.)
- Paste in the “download format MR” tab.
- Format MR page for printing
 - 1. “Find all” for “institution.”

2. Replace all "institution" with "inst. Make note of the number of studies changed in the Check List tab.
3. Decrease the width of "confirmed by." [J] to 3.00
4. Reformat cells under column header name, "scan date." [C]
 - a. Data column should be formatted to "dd/mm/yy"
5. Remove column with header name, "Phase ID." [E]
6. Remove column with header name, "Images downloaded & components confirmed during previous upload." [G]
7. Remove column with header name, "Components Confirmed during Previous Upload." [G]
8. Remove column with header name, "comments." [I]
9. Change fill color for all columns with the header name "analyzable" to "light yellow" [J, L, O, R, T, V, X, Z, AC, AE, AG, AI, AK].
10. Change fill color for columns with the header names of "Diffusion." "T2* Perf", "T1 Perm Perf", "Spec Sing", "DTI" to "light grey" [S, U, W, and Y respectively].
 - a. "Save as" date of OBDMC email.

5b - Compliance Assessment Preparation - PET

- Return to *Internet Explorer* and the web report.
- Mouse-click the "click here" link attributed to "To sign-off downloaded PET studies on OBDMC server, please click here." A new browser tab will open.
- Highlight the entire spreadsheet **including** headers, and copy.
- Return to Excel
- Paste PET Data in the "Download Raw PET" tab.
 1. Be sure that data is pasted in the first free cell of the first column. [A1]
 2. The drop-down menus the data may take a few minutes to appear.
- Once loaded, copy the PET Data from the "Download Raw PET" tab.
- Paste in the "Downloaded Format PET" tab.
- Save

I. COMPLIANCE ASSESSMENT



II. - Compliance Assessment

1 - Meetings

- There are three types of scans in each download:
 1. Head and spine MR imaging
 2. Diffusion, Perfusion and Spectroscopic Imaging
 3. PET imaging
- Each type of scan requires the review of a different specialist.
 1. Tina Young Poussaint, MD
 - Call/email and schedule an appointment to meet.
 2. Sridhar Vajapeyam Ph.D.
 - Call/email and schedule an appointment to meet.
 3. Nuclear medicine physician
 - Copy “Download Format PET” spreadsheet and paste it into an email.
 - 1) If PET studies were downloaded via eFilm, he will view images via a pre-existing sharing function in eFilm.

2 - The Compliance Assessment Worksheet

- Filling out the component portion of the sign-off sheet—
 1. Components received by the NIC should match those sent by the institution.
 - If this is the case, check the box.
 - If this is NOT the case, cross out the institution and confirmation. Write in the corrected value.
 2. If all components are present—
 - Write “all” in the column with the header name, “Images downloaded & components confirmed.”
 - Write “no” in the column with the header name, “Re-upload needed?”
 3. If not all components are present—
 - Write “some” in the column with the header name, “Images downloaded & components confirmed.”
 - The study may need re-uploading, depending on the component missing. Check “Tables 7 and 8: PBTC Protocols”, to see which components are mandatory for which protocol.

4. If none of the components are present—
 - Write “none” in the column with the header name, “Images downloaded & components confirmed”.
 - Write “yes” in the column with the header name “Re-upload needed?”
5. If Components are present but not listed, hand-write a comment stating such—
 - Filling out the analyzability portion of the sign-off sheet:
 - 1) If a component is analyzable, check the box.
 - 2) If a component is not analyzable, write “no”
 - Scans that are not analyzable do not require re-upload.
 - Comments
 1. Comments should be made on the PBTC Assessment Sheet and transcribed during the sign-off process.
 2. Comments should be separated into “OBDMC Comments,” “Site,” and “NIC” comments.
 - OBDMC – Notes to command the attention of the OBDMC
 - Site - Notes to command the attention of the Sites themselves.
 - NIC – Notes for internal use only

III. Sign-off

1 - Completed Compliance Assessment Forms

- All three scan types must be reviewed by the appropriate specialist prior to sign-off.
 - MR
 - Diffusion/Perfusion/Spectroscopy
 - PET
- The completed Compliance Assessment Worksheet should make note of the following:
 1. The download received is compliant with the study list provided by the OBDMC.
 2. The studies are compliant with their respective protocols.
 3. Studies that are present are analyzable.
 4. Missing or incomplete studies that require a re-upload request.
 5. Itemized comment list of any incidental cases that may have been downloaded but not tracked by the sites.

2- VPN Client Access

- All download procedures require an active VPN connection between St. Jude's OBDMC and Boston Children's Hospital, NIC.
- Open *Cisco AnyConnect Secure Mobility Client*
 2. Pop-up dialog box will appear. Click "Connect"
A second dialog box will open requesting: "Please enter your St. Jude User ID and Password"
Enter Credentials
This will trigger a two-factor security protocol.

 3. Successful input of two-factor security credentials will result in an additional pop-up dialog box.
"Welcome to St Jude's Vendor Client VPN."
Click "Accept" button.

3a Sign-off Procedure for MR/Diffusion/Perfusion/Spectroscopy studies

- Open Internet Explorer
- Open favorite site: "PBTC Web Report"
http://10.38.48.102/PBTC_WebReport/I8M1A3G9E7D1U6K2E9/default.html
- Log-in
 1. OBDMC has provided personal usernames and passwords. Mouse-click the "click here" link attributed to "To sign-off downloaded MRI/MRD/MRP/MRS/CT studies on OBDMC server, please click here" on the OBDMC web report.
- A new browser window will open.
- Transcribe the data collected on the Compliance Assessment Worksheet during the Compliance Assessment Meetings into the component portion of the sign-off web report.
- If *all* of the components uploaded by the institution are confirmed with institution's information, please select "yes, all" in the column with the header name, "Images downloaded & components confirmed."
 1. By selecting "yes, all" the "yes" response self populates to every "component" column offered on the web report.

2. Be aware that by selecting “yes, all” you are self-populating the “Re-upload needed?” column with a “no” response.
 3. When a “yes, all” selection does not self populate the “analyzable” column, it will require manual population.
- If *some* of the components uploaded by the institution are confirmed with institution's information, please select "yes, some" in the column with the header name, “Images downloaded & components confirmed.”
 1. By selecting “yes, some” you need to manually populate each “yes/no” drop-down menu for each component column on the web report.
 2. Be aware that by selecting “yes, some,” the “Re-upload needed?” column will not self-populate and thus, will need to be manually populated.
 - The study may need re-uploading depending on the component and the protocol. Check “Tables 7 and 8: PBTC Protocols” to see which components are mandatory for which protocols.
 3. When a “yes, some” selection does not populate the “analyzable?” column, it will require manual population.
 - If *none* of the components uploaded by the institution are confirmed with institution's information, please select "no, none" in the column with the header name, “Images downloaded & components confirmed.”
 1. By selecting “no, none,” you are automatically populating the “no” to every component column offered on the web report.
 2. Be aware that by selecting “no, none,” you are self-populating the column with the header name “Re-upload needed?” with a “yes” response.
 3. A “no, none” selection will self-populate the “analyzable?” columns to “no.”
“No, none” selection requires a reason comment for reupload comment.
 - If components are present, but not listed by the OBDMC, hand-key an NIC comment in the “comments” column stating such.
 - Click the “sign-off neuro-imaging studies downloaded from OBDMC Server” button at the very bottom of the MRI/Diffusion/Perfusion sign-off page.
 1. Blank value will result in an error message.
 - A new browser window will open with a summary of the just submitted data.

3b - Update Download/Sign-off Excel for MR/Diffusion/Perfusion/Spectroscopy

- Open Excel

- File open; [C:\PBTC Download-Signoff.xls]
 1. File should open to the “Download Raw MR” tab.
 2. Select “Sign-off MR” tab.
- Return to “Internet Explorer” and the web report submission summary page.
- Highlight the most recent data, omitting the header rows.
- Right mouse-click to copy.
- Return to Excel file [PBTC Download-Signoff.xls]
- Paste the new data into the left uppermost free cell. [A4]
- Save.

4a - Sign-off Procedure for PET Studies

- Open Internet Explorer.
- Open favorite site: “PBTC Web Report.”
- http://10.38.48.102/PBTC_WebReport/I8M1A3G9E7D1U6K2E9/default.html
- Log-in
 1. OBDMC has provided personal usernames and passwords.
- Mouse-click the “click here” link attributed to “To sign-off downloaded PET studies on OBDMC server, please click here.”
- If the study was received from the OBDMC by the NIC, select “yes” in the column named “Images downloaded & confirmed.”
 1. Manual population of “Re-upload needed?” & “PET scan analyzable?” required.
- If the study was not received from the OBDMC by the NIC, select “no” in the column named “Images downloaded & confirmed.”
 1. Self populates “yes” for “Re-upload needed?” and “no” for “PET scan analyzable?”
- Comments added in designated column as needed.
- Click the “Sign-off Neuro-imaging studies downloaded from OBDMC Server” button at the very bottom of the PET sign-off page.
 1. Blank values will result in an error message.
 2. A new browser window will open with a summary of the just submitted data.

4b - Update Download/Sign-off Excel PET

- Return to Excel.
- File open; [C:\PBTC Download-Signoff.xls]
 1. File should open to the “download MR Raw” tab.
 2. Select “Signoff PET” Tab.

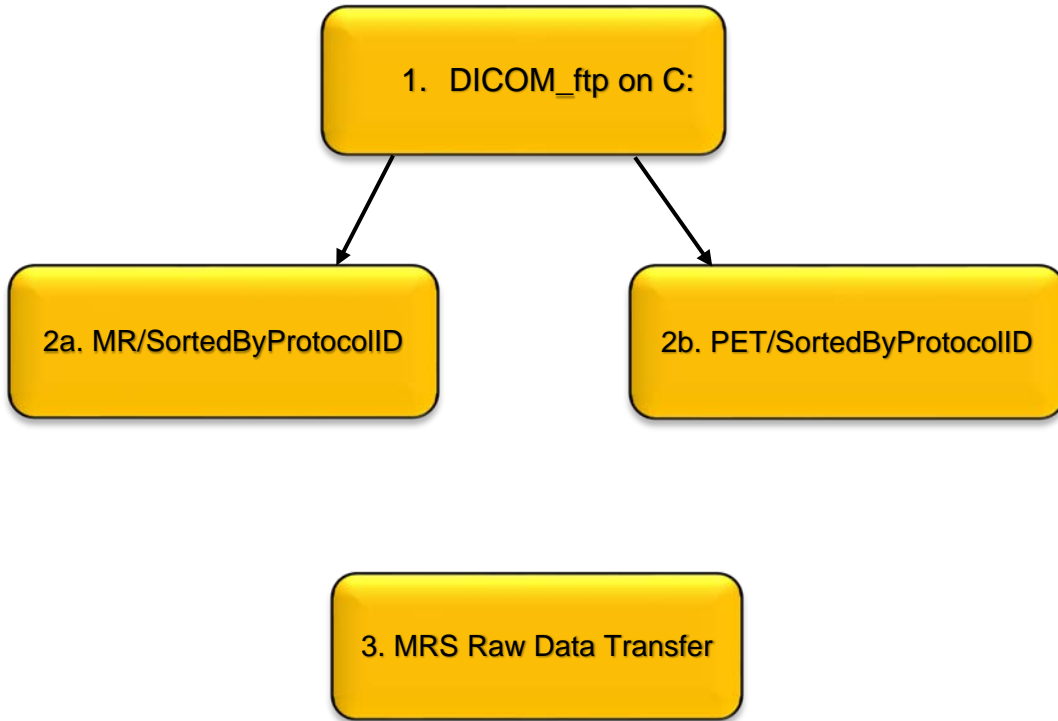
- Return to Internet Explorer and the web report submission summary page.
- Highlight the most recent data, including the header rows.
- Right mouse-click to copy.
- Return to Excel file [PBTC Download-Sign-off.xls]
- Paste the new data into the left uppermost free cell. [A1]
- Save.

5 - Update Protocol Spreadsheets - MR

- Open Internet Explorer.
- Open favorite site: "PBTC Web Report."
 1. [http://10.38.48.102/PBTC_WebReport/I8M1A3G9E7D1U6K2E9/default.html]
- Log in to the *PBTC Web Report*.
 1. OBDMC has provided personal usernames and passwords.
- Locate the "drop-down" menu and "view" button associated with "To view MRI/MRD/MRP/MRS studies sent to OBDMC and downloaded to NIC, in Excel format, select protocol."
 1. Each drop-down menu option will open an Excel file listing of all studies obtained for that protocol by accession number.
- Go to \\rc-fs.tch.harvard.edu\rad-poussaint\Public\R40300\
 - Username: **[Insert Here]**
 - Password: **[Insert Here]**
- Select folder named, "PBTC Protocol Spreadsheets"
- Contained within each protocol-specific folder is a spreadsheet for that protocol:
 - [{protocol number} PBTC-MR-image-Studies-list.xls]
 - 1. Be aware that some protocols have more than one run, or phases.
 - 2. An additional phase will be represented by a lower case Roman numeral directly following the {protocol number} in the file name. Ex: 014ii = Protocol 14, Phase 2
 - 3. A phase breakdown list can be found on the F:\ Drive of the Workstation [NIC Download Resources\Phase Information]
- Updating the spreadsheets
 1. Compliance Assessment Worksheet
 2. Select the first protocol/accession number listed on the Compliance Assessment Worksheet.
 3. \\rc-fs.tch.harvard.edu\rad-poussaint\Public\R40300\
 4. Open the Excel spreadsheet for that protocol.
 5. Select the dated tab, if the spreadsheet does not automatically open to that tab.

6. OBDMC WebReport
 7. Select that protocol on the drop-down menu of the OBDMC Web Report.
 8. View.
 9. A new browser window will open as well as a “file download – security warning.”
 10. Open. This will open the OBDMC version of the spreadsheet in the new browser window.
 11. Using the Compliance Assessment Worksheet as a guide, select the entire row corresponding to the protocol/accession number/date combination for the study in that download.
 12. Copy.
- Return to \\rc-fs.tch.harvard.edu\rad-poussaint\Public\R40300\
13. [Return to \\rc-fs.tch.harvard.edu\rad-poussaint\Public\R40300\](https://rc-fs.tch.harvard.edu/rad-poussaint/Public/R40300/)
 14. Paste the new row in the first open row of the dated tab.
 15. Continue copy/paste until each newly downloaded entry for that protocol is completed.
 16. Rename the worksheet tab on the spreadsheet to reflect the day the update took place.
 17. Continue this process for each protocol, until the entire download has been reflected on the spreadsheets.

IV. SORTING IMAGES



IV. - Sort

1 - File Backup – FTP

- Open the two local browsers on the iMac machine:
 1. C:\PBTC_Download\DicomFTP
 2. Poussaint on RC-FS(RC-FS.tch.harvard.edu)

2a - Move to the NIC Server – MR

- Copy files from the workstation into respective protocol specific folder on the server.
- Repeat until all files in workstation have been moved to the server.

2b - Move to the NIC Server – PET

- Move files from the workstation into respective protocol specific folder on the server.
- Repeat until all files in workstation have been moved to the server

MRS Raw Data Transfer

Contact Person: Sridhar Vajapeyam, PhD 617-355-7870;

Email: sridhar.vajapeyam@childrens.harvard.edu

Please note all sites should do a screen save of the MRS spectrum with the ratios displayed on the image.

1.) GE Scanners

- The spectroscopy raw data files are stored in the directory /usr/g/mrraw.
- Open a C shell and go to the directory /usr/g/mrraw by typing the command "cd /usr/g/mrraw."
- List the files in the directory by typing "ls -l."
- You will see several files with names like Pxxxxx.7.
- You will also see the date and time the files were created.
- Pick the right files based on the date and time the MRS study was conducted and copy them to a separate directory and then transfer them to OBDMC of the PBTC.

2.) Siemens Scanners

- The Syngo Database will list the spectroscopy raw data files associated with a study.
- Export these files to a new folder and then transfer them to OBDMC of the PBTC.
- Since Sonata System has no means of writing any data other than patient data (in DICOM format) into a CD ROM, you would have to first export the raw data to a temporary directory. You will then ftp this file to a PC or a Unix workstation for further processing. The data is in Siemens 'rdx' format following export.

Exporting data:

- a. Drag raw data into the "spectroscopy task card" just as you would when processing spectroscopy data.
- b. Click on "options" on the menu bar and then choose "export raw data".

- c. You will be asked for a directory and a file name to export the data.
- d. Normally you would use the "C:\temp" Directory. Data now is exported.
ftp data:
 - a. First log into Windows NT system by holding 'CTRL" and "Esc" keys > together. This will allow you to get access to the Microsoft Windows > environment.
 - b. Click on "start" button on the lower left corner of the screen, click on "advanced user" if you have not logged into the NT systems previously. This will give you a prompt window for your password input. Factory default password is "meduser1" unless it has been previously altered.
- c. After you log into the NT systems, hit "CTRL" and "Esc" simultaneously again. Go to "start" then "programs" and the "command prompt." This will open up a DOS window with a prompt "C:\\". Change to "temp" directory (or other directory you created when you export your raw data) by typing "cd temp."
- d. You can now ftp your data out to other PC or workstations. Do not forget to set to "binary" mode when you ftp or your data will be garbled.
- e. Example: "ftp 123.45.678.99" (connect to your ftp server PC or unix system) (enter user name/password) "bin" (change from ASCII mode to binary) "put file name" (upload data) "quit."

3.) Phillips Scanners

- Raw spectroscopy data and the corresponding header information are stored as .SDAT and .SPAR files associated with the patient identifier.
- The localizer image data and header are stored as .REC and .PAR respectively.
- Transfer all these files for each spectroscopy study into a separate folder and then transfer to OBDMC of the PBTC.

Transfer to OBDMC of the PBTC MRS data will require an ftp connection between the site's scanner workstation and the PBTC laptop. Once the files reach the PBTC laptop at the site, then the CRA at the site can ftp it over the secure channel to OBDMC of the PBTC.

IX. APPENDICES OF NEUROIMAGING STUDIES PROTOCOLS AND FORMS

APPENDIX A: PBTC NIC MR PROTOCOLS OF BRAIN AND SPINE

A1. Data Form Completion and Entry

All images are read by the NIC neuroradiologists. The NIC neuroradiologist completes the PBTC MRI compliance and data form for the brain and spine, and the forms are provided to Katherine Rosen at the Institutional Centers for Clinical and Translational Research (ICCTR) for data entry through the PBTC web-based data management system. These data are managed centrally for statistical analysis by the PBTC OBC.

APPENDIX B: PBTC NIC MRI QUALITY ASSURANCE PROCEDURES

A complete report of the current state of MRI QC with quantitative listings of the results from each site is compiled and a running update of the overall QC report is handled by the Institutional Centers for Clinical and Translational Research (ICCTR) at Boston Children's Hospital. Dr. Mulkern receives the completed forms from each site as they perform tests. He archives the hard copy, performs a close inspection of each report to identify errors or outliers in the form; then the new data is entered by the ICCTR into the QC report. Data and statistics associated with each of the seven tests for each site are maintained. Regular meetings (monthly or more) between Dr. Mulkern and the ICCTR personnel have been established to maintain an active QC MRI program. Sites will be notified when action level values exceeding 15% of the mean for any measurement are noted by the NIC. Each site should follow its own institutional procedures in assessing and/or repairing the scanner in question.

Sites should also have a spectroscopy phantom as supplied by their manufacturer. In the case of General Electric sites, the phantom is referred to as the Braino phantom as it contains concentrations of the major metabolites similar to that found in the human brain. At least quarterly, this phantom should be scanned and the values for the three resonances NAA, Cho and Cr associated ratios should be recorded in the PBTC QA form

The primary quality control testing should be done quarterly using the American College of Radiology (ACR) MRI test phantom which is also used for the accreditation process of MRI systems. Each site should purchase the phantom which comes with manuals on how to scan and analyze the subsequent data. For ACR phantom purchase, please contact:

J.M. Specialty Parts
11689-Q Sorrento Valley Rd.
San Diego, CA 92121

B1. Typical Report:

The ACR phantom was imaged according to the guidelines of the ACR pamphlet “Site scanning instructions for use of the MR phantom” and subsequent measurements were made from sagittal and axial images acquired with T1-weighted and T2-weighted spin echo sequences.

B2. Test Procedure

Seven specific tests are performed from a scanning session that should last less than 20 minutes. A description of each exam and analysis as performed here at Boston Children’s Hospital is provided below. Note that all 7 tests provided results which were within the acceptable limits of image quality specified by the ACR which will also be used as the PBTC criteria for acceptable scanning.

Test 1: Geometric Accuracy

Linear measurements of the dimensions of the phantom along several directions are made and compared with known dimensions of the phantom. Measured values must be within ± 2 mm of known dimensions.

Results:

- a) end-to-end-sagittal view, localizer slice, measured value = 147 mm, actual value = 148 mm.
- b) top-to-bottom axial view, slice 1, measured value = 189 mm, actual value = 190 mm
- c) left-to-right axial view, slice 1, measured value = 189 mm, actual value = 190 mm
- d) top-to-bottom axial view, slice 7, measured value = 190 mm, actual value = 190 mm
- e) left-to-right axial view, slice 7, measured value = 190 mm, actual value = 190 mm
- f) diagonal 1, axial view, slice 7, measured value = 190 mm, actual value = 190 mm
- g) diagonal 2, axial view, slice 7, measured value = 189 mm, actual value = 190mm

Test 2: High Contrast Spatial Resolution

Three pairs of 4 x 4 arrays of 1.1 mm, 1.0 mm and 0.9 mm holes are imaged and counted with imaging sequences having a 1 mm spatial resolution specification. The number of distinguishable holes in each array are identified.

Array 1 (1.1 mm holes) – all holes identified

Array 2 (1.0 mm holes) – all holes identified
Array 3 (0.9 mm holes) – only ¼ holes identified

Test 3: Slice Thickness Accuracy

The slice thickness insert of the phantom consists of two crossed ramps which yield estimates of the actual vs. proscribed slice thickness of 5 mm. Length measurements of the top and bottom ramp signal intensities were 63 mm and 41 mm respectively from which the actual slice thickness is calculated using the formula

$$\text{Slice thickness} = 0.2 \times (63 \times 41 / (63 + 41)) = 4.97 \text{ mm}$$

Which is well within the specified range of 5.0 ± 0.7 mm required for acceptance.

Test 4: Slice Position Accuracy

Slices 1 and 11 are aligned with the vertices of crossed 45° wedges so that when perfectly aligned, two black bars will appear next to each other in each of the images of slice 1 and 11. For perfect slice position, the bars will have equal length. If the difference between the bar lengths is less than 5 mm, then the center of the slices are within 2.5 mm of the prescribed locations and within tolerance. The bar length differences in slices 1 and 11 were approximately 3 mm, well within tolerance (less than 5 mm) for this measurement.

Test 5: Image Intensity Uniformity

A uniform region of the phantom (axial slice 7, 19,849 mm² area) was selected and two regions-of-interest (ROI's), 100 mm² each, with the highest and lowest signal intensities were identified. Signal intensities from these two ROI's were used to calculate the percent integral uniformity (PUI) through the equation

$$\text{PUI} = 100 \times (1 - (\text{ROI}_{\text{high}} - \text{ROI}_{\text{low}}) / (\text{ROI}_{\text{high}} + \text{ROI}_{\text{low}}))$$

The ROI_{high} and ROI_{low} were measured as 1374 and 1227, respectively, yielding a PUI value of 94 %. This is above the minimum PUI value of 87.5 % required for acceptance.

Test 6: Percent Signal Ghosting

The large ROI identified for image intensity uniformity (Test 5) is used to estimate signal intensity within the ACR phantom (ROI_{large}). Four additional measurements are made in the air outside of the phantom to estimate noise values along both the frequency and phase encode dimensions. Ghost signal occurs only along the phase encoding direction so that the ghost signal is calculated as

Ghosting ratio = (left + right – top – bottom)/(2 x ROI_{large})

Measurements were 1321, 11.1, 10.9, 17.8 and 16.8 for the large, top, bottom, left and right ROI's respectively where the left and right were the phase encode noise measurements containing the ghost signals. The ghosting ratio was thus calculated as 0.005 which is well below the 0.025 limit specified for acceptance.

Test 7: Low Contrast Object Detectability

Slices 8 – 11 of the ACR phantom contain 10 spokes each containing 3 low contrast objects per spoke with contrast decreasing from 5.1 %, 3.6 %, 2.5 % and 1.4 % for slices 11 – 8, respectively. One counts the number of spokes for which all three objects can be seen in each slice and sums the number of spokes so-counted through all four slices (a spoke is not counted if any one of the three objects are not visualized). From the T1 spin echo scans, 36 spokes were counted and for the T2-weighted spin-echo sequence 37 spokes were counted. This far exceeds the 9 spokes required per scan for acceptance.

B3. Data Form Completion and Entry

Sites should complete the QA form or submit ACR certificate to Radiology Imaging Data Analyst/Research Data Coordinator in the BCH Department of Radiology.

B4. Reporting and Follow-up

Sites will be notified when action level values exceeding 15 % of the mean for any measurement are noted by the NIC. Each site should follow its own institutional procedures in assessing and/or repairing the scanner in question.

B5. Questions

For any questions regarding the implementation of the quality assurance procedures, sites should contact: Robert Mulkern, Ph.D. at 617-355-3737, email: rmulkern@yahoo.com

APPENDIX C: PBTC NIC PET FACILITY PROCEDURES

GE ADVANCE

C1. NEURO: FDG Brain Tumor Protocol

Patient Prep: Adult- NPO for 4 hours prior to F-18 FDG injection (water encouraged).
Infant- NPO for 2 hours prior to F-18 FDG injection (water encouraged).
I.V. or hep lock is necessary along with a possible sedation order.

Radiopharmaceutical: F-18 FDG

Dose: Determined by patient weight with minimum and maximum values.

Adult- 5 - 15 mCi
Pediatric- 0.5-10.0 mCi (0.143 mCi/kg)

Acquisition mode: 3D

Acquisition time: 6 mins

Attenuation correction: Performed using either a calculated method, a measured method with 3 min transmission scan with segmentation applied or CT if the study is acquired on a PET/CT scanner.

C2. Method

- 1) Patient is interviewed for pertinent medical history and discussion of PET procedure.
- 2) Injection of F-18 FDg is made with the patient in supine position. After the injection the room lights are dimmed. The patient is instructed to stay awake but quiet. Approximately 80% of the glucose localization occurs in 20 minutes, so movement and/or sedation may proceed 20 minutes after injection.
- 3) Patient is asked to empty bladder after injection.
- 4) Imaging begins at 40-60 minutes post F-18 FDG injection.
- 5) Patient is positioned in PET head holder.
- 6) Patient is asked to empty bladder post scanning; hydration and frequent bladder emptying are encouraged.
- 7) Any variation in the above technique should be brought to the attention of the PET attending physician.
- 8) **Any possibility of pregnancy and/or breastfeeding must be ruled out prior to injection/inhalation of radioactive material.**

C3. Data Form Completion and Entry

All images are read by the NIC PET nuclear medicine physician and physicist in conjunction with the NIC neuroradiologist. The NIC PET physician completes the PBTC PET compliance and data form and the form is provided to the Clinical Research Center for data entry into the PBTC web-based data management system. These data are managed centrally by the PBTC Biostatistics and Operations Center.

C4. Questions

For any questions regarding the PET procedures, sites should contact Frederic Fahey at (617) 355-2809 or e-mail at frederic.fahey@childrens.harvard.edu.

Data for calculation of SUV, i.e. injected activity, time of injection, time of scan, patient weight and patient height as well as additional parameters (see PET support form 14) are recorded for each PET exam and uploaded with the study to the OBC.

APPENDIX D: PBTC NIC CASE REPORT FORMS

| | |
|-----------|---|
| Form 100a | MRI Brain Data |
| Form 100b | MRI Brain Data |
| Form 2 | MRI Quality Assurance |
| Form 3 | Retired: No longer in use |
| Form 4 | PET Brain Data |
| Form 5 | PET Quality Assurance |
| Form 6 | MRI Spine Data |
| Form 7 | Retired: No longer in use |
| Form 8 | Retired: No longer in use |
| Form 9a | MRI Brain Leptomeningeal Data |
| Form 10 | Retired: No longer in use |
| Form 11 | Retired: No longer in use |
| Form 12 | Retired: No longer in use |
| Form 13 | Retired: No longer in use |
| Form 14 | PET Support Data |
| Form 15 | PET Phantom Acquisition Form |
| Form 16 | Merged: Now part of Form 1a |
| Form 17 | Fusion Volumetrics |
| Form 18 | MRI Brain Permeability |
| Form 19 | Site Visit Mandatory Reporting Form |
| Form 20 | ⁶⁸ Ge ACR Phantom Acquisition Form |
| Form 21 | Spinal Tumor Volume |
| Form 22 | Comments Form |
| Form 23 | RECIST Measurements |
| Form 24 | Macdonald Criteria |
| Form 25 | Diffusion Tensor Imaging |
| Form 26 | MR Contrast Survey |
| Form 27 | ADC Histogram Analysis |
| Form 28 | MRI Brain Permeability |
| Form 29 | ADC Histogram Quality Assurance |
| Form 30 | sFDM QA & Data Form |
| Form 32 | 026 Quality Assurance Form |
| Form 33 | Serial Tumor Measurements |
| Form 34 | Medulloblastoma Evaluation |
| Form 35 | Post Radiation Assessment |

V. Guidelines for Reading and Interpreting Imaging Studies

The NIC is responsible for image analysis of all PBTC research neuroimaging studies. Each study is reviewed by 1 Neuroradiologists from the NIC and the final interpretation of results reached by consensus.

Before image analysis, imaging studies are evaluated for readability and compliance with the protocol and the protocol compliance form is completed by the data volumetric analyst and data analysis engineer in consultation with the neuroradiologist.

The standard FLAIR, T2, and gadolinium sequences are sent to the Vitrea workstation (Vital Images, Plymouth, MN) and volumetric analysis is done. The data volumetric analyst consults with one of two neuroradiologists to determine the tumor site and regions of interest to be measured. Automated segmentation software defines the tumor regions on FLAIR or T2 images and nonenhancing and enhancing tumor regions on gadolinium T1 axial images. The perfusion, diffusion and MRS components of each study are transferred from the PC workstation to a dedicated workstation for image analysis (see data form MR). After reviewing the post-analysis data, the information is backed up on the NIC workstation, research computing server and a dedicated backup server system through BCH Research Computing.

VI. Data Management Procedures

Data is collected on hard copy forms by NIC data analysts, NIC nuclear medicine physicist/physician and neuroradiologists at the time of image analysis. A dedicated RedCap database is used to compile data. The NIC Research Coordinator, Katherine Rosen, ensures that all necessary data are collected in a timely and efficient fashion. The study coordinator reviews all hard copy data forms and completes data entry at the Institutional Centers for Clinical and Translational Research (ICCTR). The data forms are entered directly through the PBTC web-based data management system and managed by the PBTC Operations, Biostatistics and Data Management Core(OBDMC). All analytic and database files are backed up daily. No patient identifiers are present in the database or on forms. Each study participant has a unique PBTC assigned study numeric study identifier that includes a site, protocol, and subject identifier.

The Department of Radiology at the NIC has its own Information and Technology (IT) dedicated staff under the leadership of Paul Lamonica who oversee the networking and security of the imaging data received. A dedicated file system on the ftp server is used to store and disseminate data. Imaging data is transferred via a secure tunnel from St. Jude's to our dedicated server. Imaging studies are backed up onto the NIC server, research computing share drive and backed daily by the Research Computing at Boston Children's Hospital under the supervision of Joshua Lopez.

VII. PBTC NIC Data Management System

The Clinical Research Information Technology Core will be used as a central location for data processing and management. Boston Children's Hospital, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Institutional Centers for Clinical and Translational Research. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap servers are housed in a local data center at Children's and all web-based information transmission is encrypted. REDCap has been disseminated for use locally at other institutions and currently supports 5,980 active consortium partners in 147 countries. REDCap software has generated over 1,563,000 projects from over 2,239,000 users. 20,821 journal articles cite REDCap. (www.project-redcap.org)

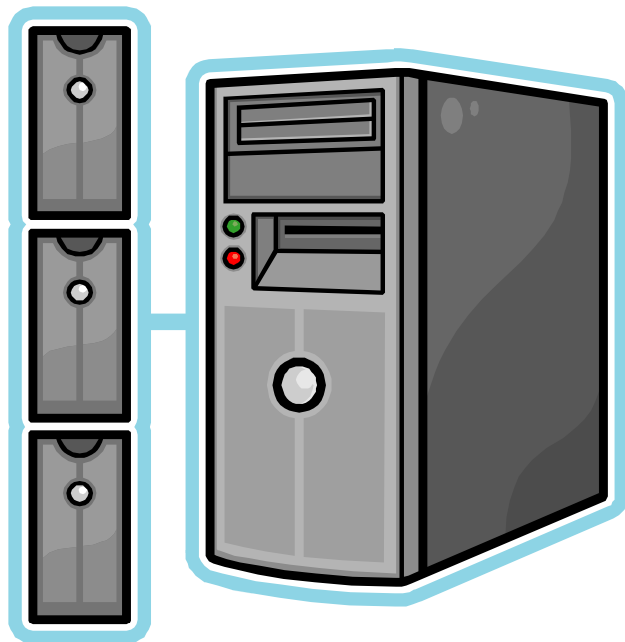
The PBTC NIC Clinical Data Management System “Users Manual” diagrammatic flow chart, and protocol matrix follows.

Clinical Data Management System Users Manual

Project: Pediatric Brain Tumor Consortium

Neuroimaging Center

PI: Tina Young Poussaint, MD



Scientific Research Information System
Informatics Team, Clinical Research Program
Boston Children's Hospital,

Data Management System (User Manual)

| | |
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Introduction

A Data Management System (DMS) is a software program of varying size and sophistication by which data collected on case report forms are stored, tracked and prepared for analysis. The data management system for this study is Web accessible and supports the following features.

- Basic Security (user authentication and authorization)
- Data Capture
 - Real-Time Validations
 - Outlier Identification
 - Read-Only Access
- Protocol Tracking
 - Custom Data Management Reports
- Audit Trails

This data management system is programmed to adhere to the operations of the study protocol (See pages 20 & 21). Clinical staff may use the DMS to track the progress and state of each case report form for each study participant. Standard data management reports will be added to the system to facilitate preparation of data for analysis.

Many of the features outlined above are described in detail in this manual. Further questions regarding DMS functionality should be directed to the clinical research specialist liaison of the Clinical Research Center office.

System Overview

Requirements

As stated previously, the DMS is a Web-based system accessible from inside the Boston Children's Hospital, intranet only. The Web site requires users to employ Internet Explorer version 8 or higher.

The data management system is accessible through the following URL.
http://redcap-qi.tch.harvard.edu/redcap_edc/

Application Security

CRC provides user access to key personnel for initial website access. Once access is granted, users will use their Children's ID and password to log in. User access to the database is determined by individual role on project.

Login Screen

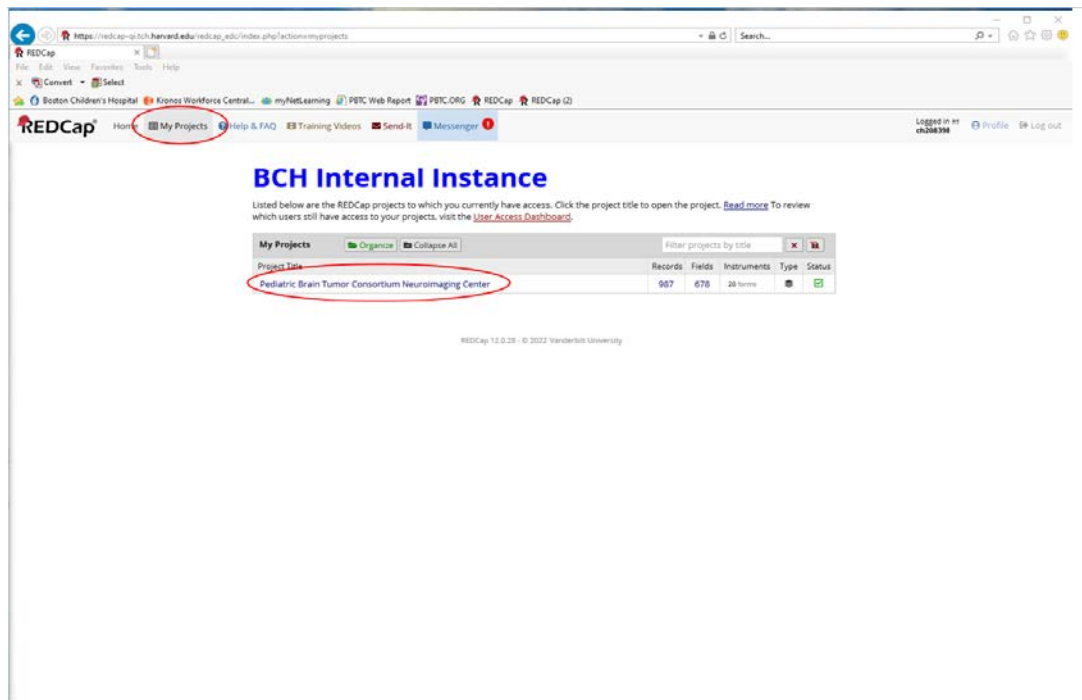
All users are directed to the Login Screen at start-up (see below).

The screenshot shows a web browser window with the URL https://redcap-q1.tch.harvard.edu/redcap_edc/index.php?user_verify=YcaU8H5F5mpqDM7MhmiY5c. The page features the REDCap logo at the top left. Below the logo, the text reads "Log In" and "This is the **INTERNAL** instance. Use your BCH Username and Password to Login." There is a link to "Submit a request for a new REDCap project". The main heading is "BCH Internal Instance" with a sub-note: "Please log in with your user name and password. If you are having trouble logging in, please contact [The Clinical Research Informatics Team \(CRIT\)](#)." The login form includes fields for "Username:" and "Password:" followed by a "Log In" button. Below the form, there are two columns of text: "Welcome to REDCap!" and "REDCap Features". The "Welcome to REDCap!" section describes the platform's capabilities and provides a link to a "brief summary video (4 min)". The "REDCap Features" section lists several key features: "Build online surveys and databases quickly and securely in your browser", "Fast and flexible", "Advanced instrument design features", "Diverse and flexible survey distribution options", and "Data quality".

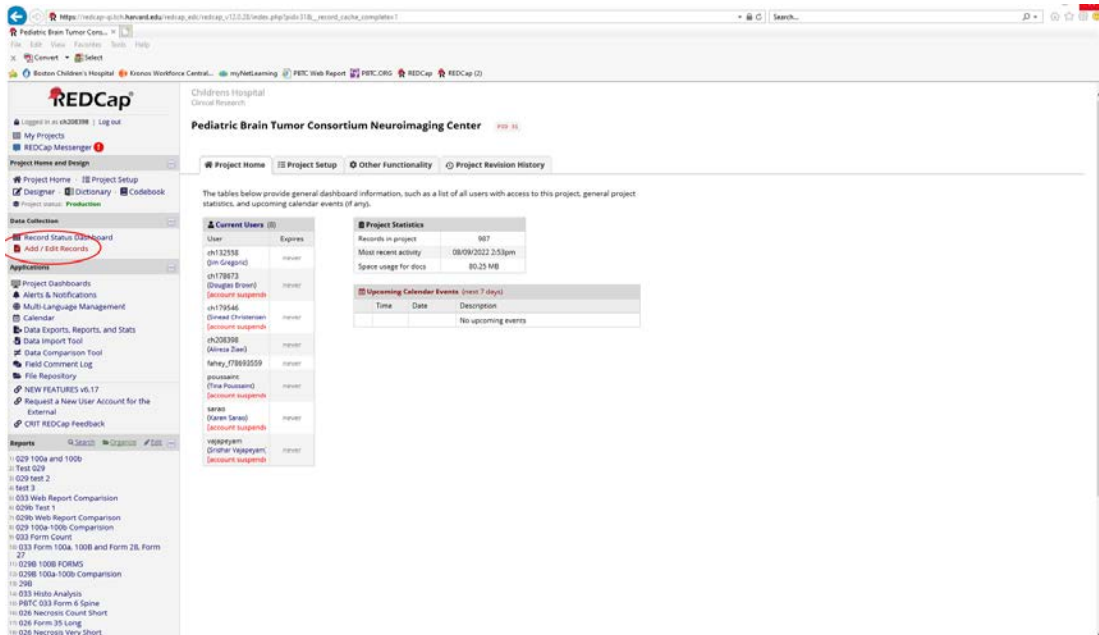
If a user has difficulty logging in, they may select REDCap Support link and request help.

Home (Portal) Screen

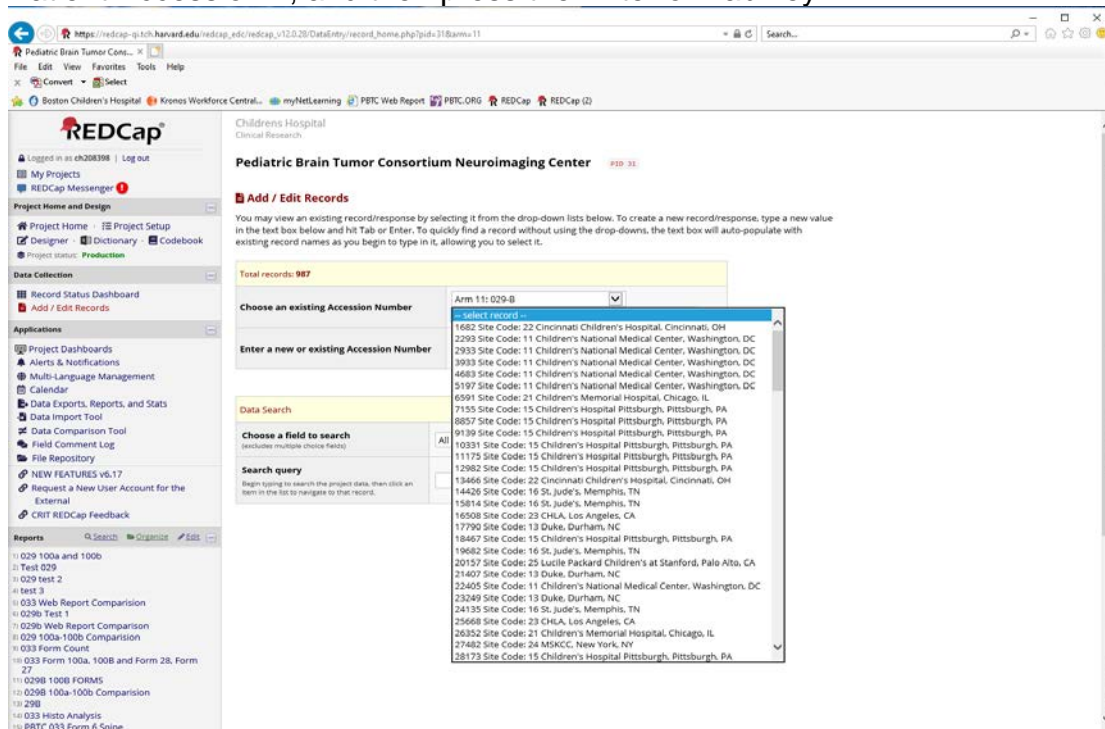
Upon logging in, the user must select the **My Projects** tab. From there, the user will click on the link labeled **Pediatric Brain Tumor Consortium Neuroimaging Center**.



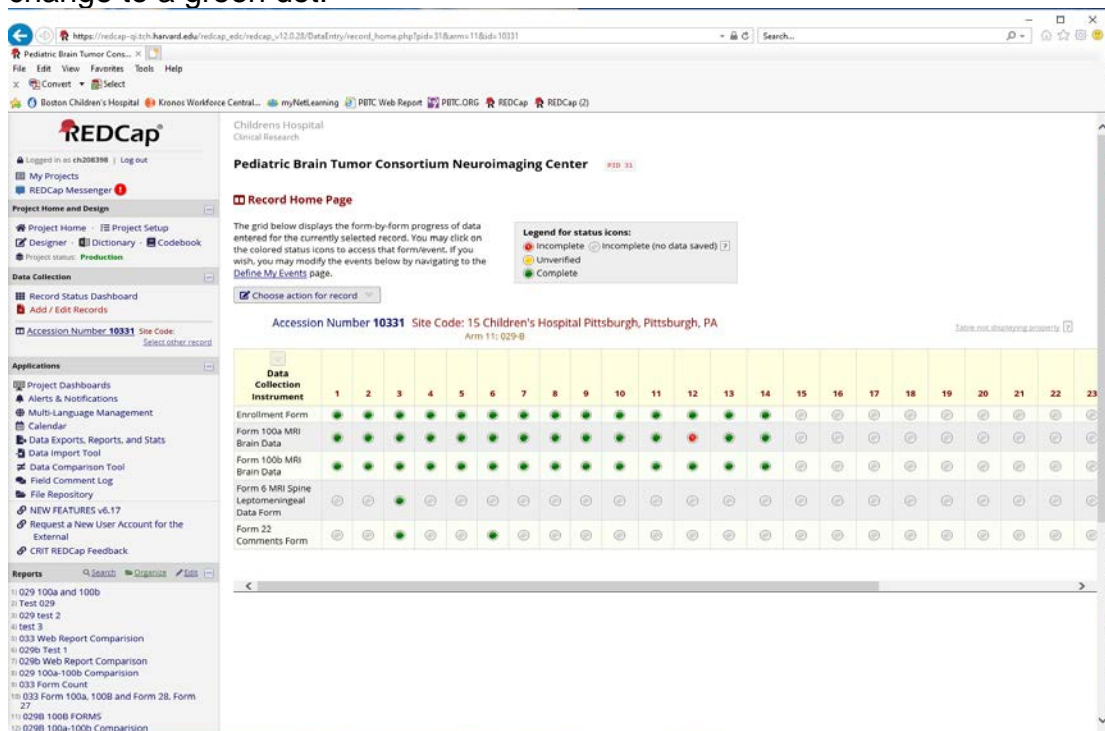
Next, the user will select the **ADD /EDIT RECORDS** link on the left side of the page.



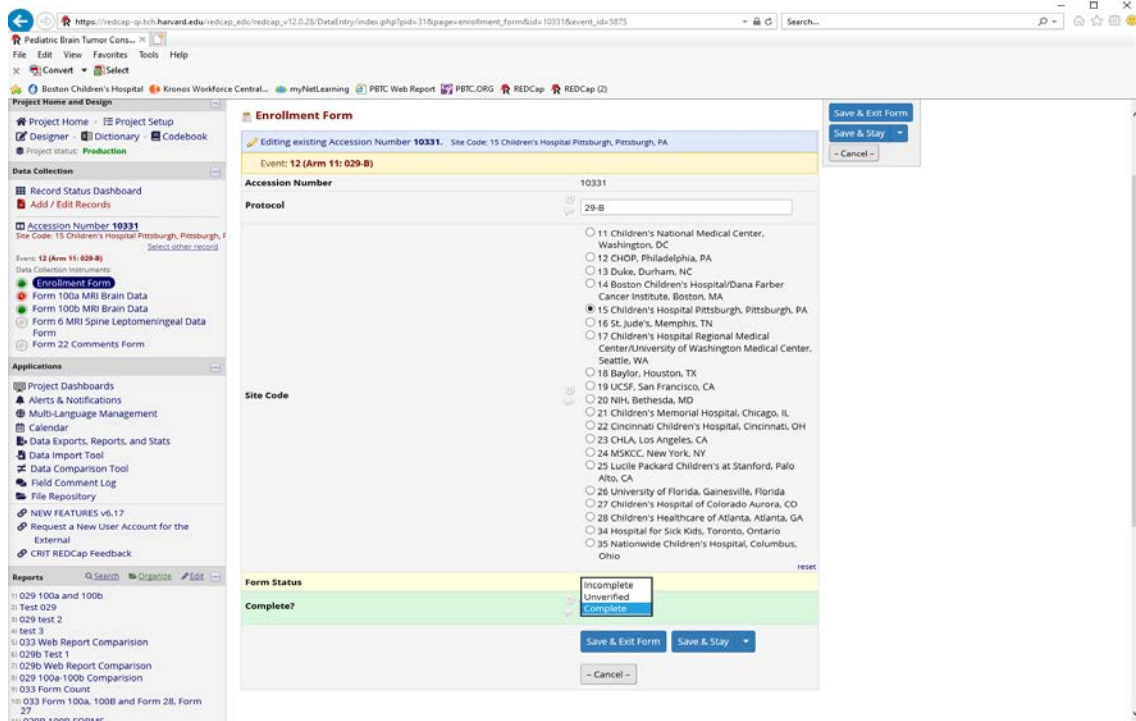
On the next screen, the user must select the arm (or PBTC Protocol), enter the Patient Accession #, and then press the Enter or Tab key.



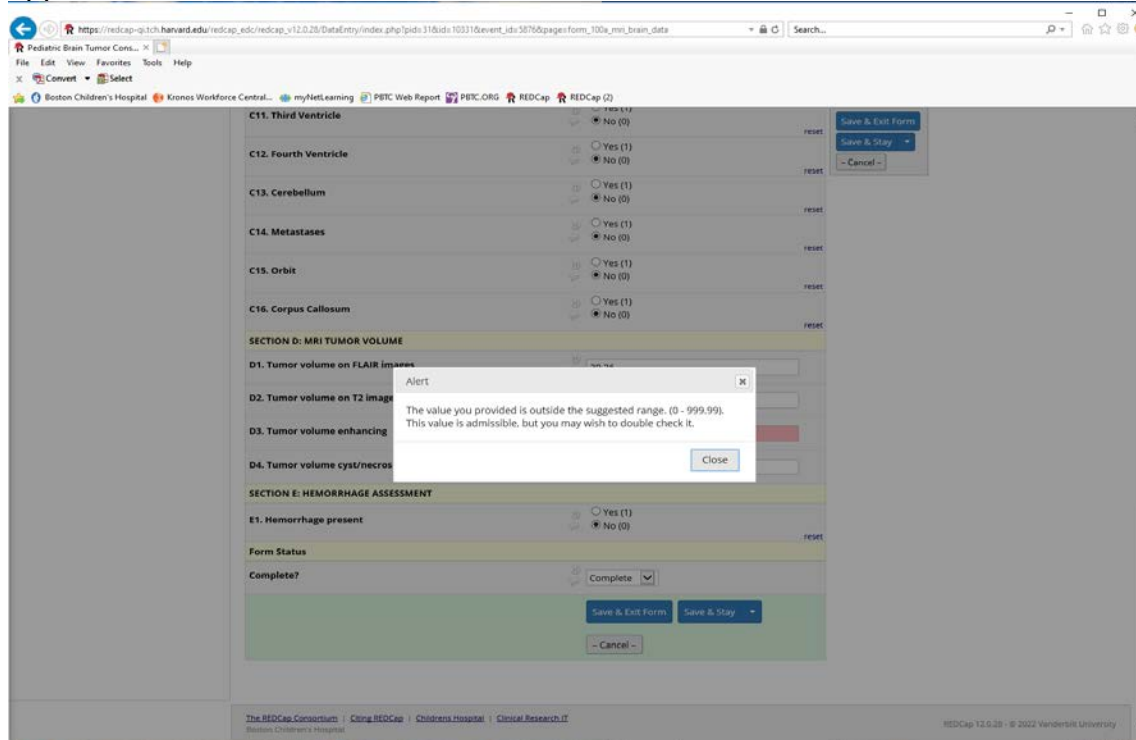
Next, the user must select the appropriate **Data Collection Instrument** (or Form) and **Event** Number for data entry. Red dots designate forms that have not been entered yet. Once a form has been entered and saved, the red dot will change to a green dot.



On the next screen, the user will be able to enter the data for the selected **Data Collection Instrument** (or Form) and **Event** Number. Once the form is entered, the user can specify whether the form is **Complete**, **Incomplete**, or **Unverified** and then click the **Save Record** button.



If an entered value is outside the specified range, a warning message will appear.



VIII. Quality Control Approaches

A. Training and Certification Requirements of the Neuroradiologist

The neuroradiologists at each site must be a Board certified radiologist with expertise in neuroimaging and/or CAQ accreditation.

B. Manuals of Operation

The NIC Manual of Operations documents all procedures or standard clinical protocols and research protocols, which address diagnostic standard protocols; intravenous contrast doses and infusion times when appropriate; image data storage; image data transfer; tumor volumetric analysis. Manuals are provided to each site for implementation of all imaging protocols and updated by the NIC throughout the study as appropriate.

C. Coordination and Communication

The NIC coordinates regular communication and meetings among the participating neuroradiologists of the Neuroimaging Committee and PET investigators of the PET Investigator Committee. This includes at least quarterly conference calls and biannual meetings as well as regular e-mail exchange for routine correspondence and questions. Dedicated consensus conferences and/or neuroradiology symposia for PET and MR investigators are held on a biannual basis at Boston Children's Hospital or PBTC meetings.

D. Site Visits

The NIC will conduct site visits as needed to each site to review procedures and compliance with all PBTC protocols. During the visit, participating sites will be expected to provide materials and answer questions directed by the NIC. An evaluation checklist will be completed at these site visits for inclusion in a Site Visit Report to the Principal Investigator and PBTC Steering Committees (see Site Visit Monitoring Report attached).

E. Reader Reliability

The reproducibility of the central image interpretation is evaluated by selecting a random 20% subsample of exams from each protocol for repeat interpretation at the NIC. All NIC neuroradiologists are blinded to the exams. Inter-rater and Intra-rater reliability is assessed by examining the percent agreement with the first reading (see Form 1b).

F. Data Quality

Regular meetings of the NIC staff occur with each download where images from the participating institutions are reviewed for routine compliance with the standardized imaging protocols set by the NIC. These data are entered into a web-based form at the OBDMC. NIC staff assess the diagnostic image quality and data integrity prior to submitting the CT, MR and PET data for analysis. Dr. Mulkern reviews the current QA protocols at each of the participating institutions including MR and MRS phantom controls in use. Compliance is insured with the QA protocols throughout the course of the study. In addition, the NIC, with the OBDMC, generates summary statistics and a report on the image quality and compliance with PBTC protocols by site and overall. These are distributed to the NC and Steering Committee for review on a biannual basis. An overview of the quality control procedures for each imaging study are as follows.

MRI Quality Control: Each site should have an American College of Radiology (ACR) phantom, which can be purchased (J.M. Specialty Parts, 11689 Sorrento Valley Rd, San Diego, CA 92121, 858-794-7200). This phantom comes equipped with a guide to performing specific tests of geometric accuracy, high contrast spatial resolution, slice thickness accuracy, slice position accuracy, image intensity uniformity, percent signal ghosting, and low contrast detectability. Each scanner used for the trial, scans the ACR phantom quarterly. These QC data sets are sent to the NIC on a regular basis where they are evaluated according to the recommendations of the ACR accreditation manual. Site scanner equipment includes Siemens, Phillips and GE scanners. A video for the MR QC process is posted on the website of the NIC: www.childrenshospital.org/research/pbtcnic Statistical data from the QA program is generated in the form of reports on an ongoing basis.

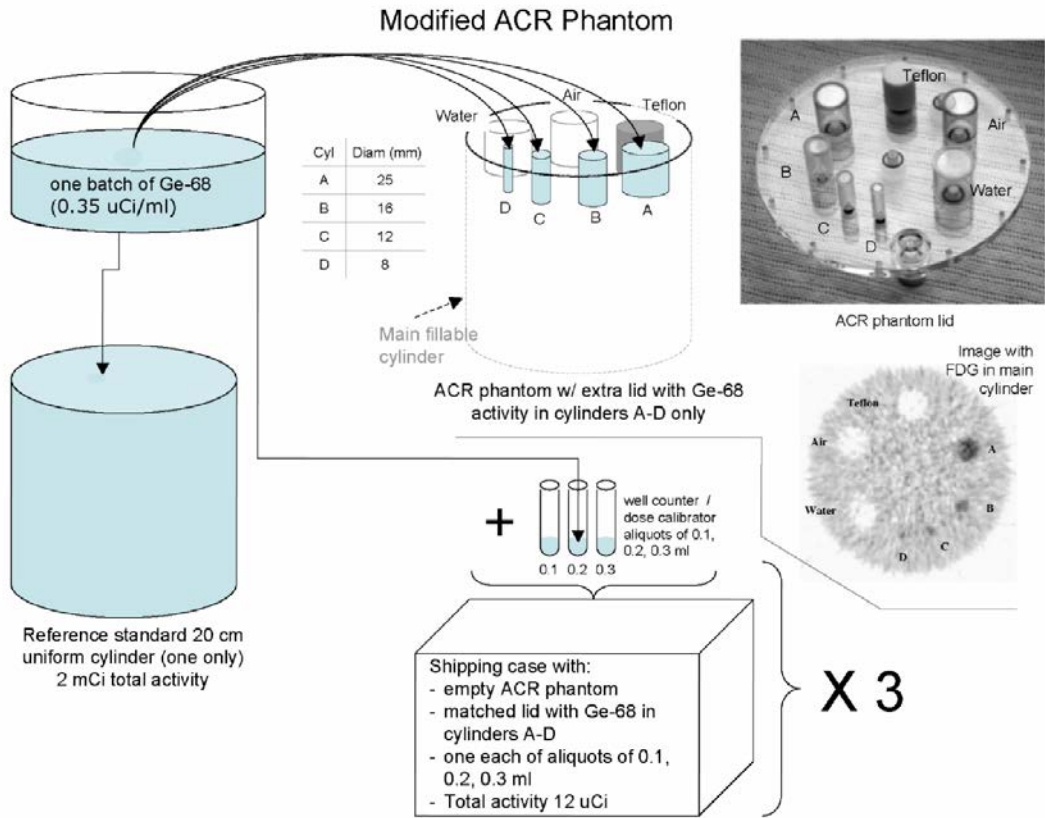
PET Quality Control: The quality control program for PET assures proper operation of all of the detector blocks and the accuracy of quantitation. Daily “blank” scans should be acquired to evaluate the operation of the detector blocks. Scanners provided by certain vendors require periodic updating of photomultiplier tubes to ensure proper operation. For General Electric scanners, an “update gains” check of the photomultiplier tubes should be performed weekly. For Siemens scanners, a “bucket setup” should be performed quarterly. Philips scanners do not require such a check. Modern PET scanners consist of thousands of small detectors and it is imperative for proper operation that their response be “normalized.” Such normalization of the scanner should be performed quarterly according to the manufacturers’ specifications. After normalization, a calibration must be performed for the scanner to be able to report the in vivo radiopharmaceutical distribution in Bq/mL or $\mu\text{Ci/mL}$. Therefore, this calibration should be performed quarterly. PET scanners are complicated devices that require regular, preventive maintenance. Such preventive maintenance should be performed quarterly.

All members of the PBTC provide quarterly reports with regards to compliance to the PET quality control program described above. These reports

require completing Form 5 (PET Quality Assurance Data Form) and sending it to the Neuroimaging Center. Each site completes a one-time analysis of a PET phantom (Form 15). Statistical data from the PET QA program is generated in the form of reports on an ongoing basis.

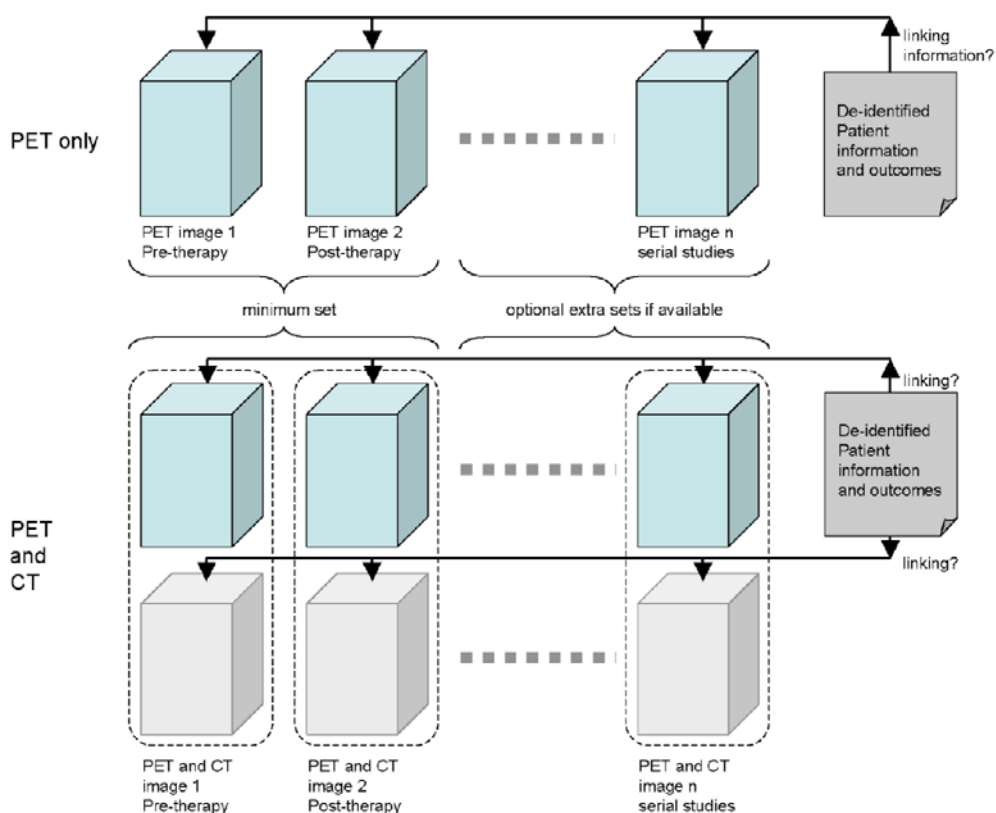
The PBTC NIC was involved in a project with Paul Kinahan, PhD, of the University of Washington and Laurence Clarke, PhD of the NIH, that entails the imaging of a 20 cm cylindrical phantom with “hot” (i.e., higher activity concentration than the background) and “cold” (i.e., lower activity concentration than the background) features. This collaborative project, jointly overseen by the *Society of Nuclear Medicine* (SNM) and the *American Association of Physicists in Medicine* (AAPM), centered on the design of a phantom made with an equilibrium mixture of $^{68}\text{Ge}/^{68}\text{Ga}$ and equipped with 4 hot features of varying size (8-25 cm) and 3 cold features (all 25 cm of different materials) incorporated into a lid that can be used with the phantom imaged in 2005.

Following an initial evaluation of the phantom and corresponding, standardized imaging protocol and reporting form, the phantom was deployed to the respective PET imaging programs of the 10 PBTC NIC sites. We asked each site to 1) image the phantom as if it were a PBTC subject; 2) report which features were visible; and 3) record the SUV values for the background as well as the 4 hot features. The data obtained from this QC procedure enabled the NIC to better understand how quantitation differed among the PBTC sites and how limits of accuracy may varied depending on which clinical application was being tested. This study was published by the *Journal of Medical Physics* (Fahey FH, Kinahan PE, Doot RK, Kocak M, Thurston H, Poussaint TY. Variability in PET Quantitation Within a Multicenter Consortium. *Med. Phys.* 2010 Jul;37(7):3660-3666).



*Image courtesy of University of Washington – Seattle

RIDER PET/CT Patient Data



*Image courtesy of University of Washington – Seattle

PET Data Analysis:

All PET imaging data acquired via a PBTC protocol is forwarded to the OBC and subsequently sent to the NIC for analysis by download or FTP.

All PET imaging data, along with their corresponding MR data, are uploaded to a multi-modality processing and review station (Hermes Medical Systems). Whether the imaging data is present and readable is determined and noted on Form 4. If the data are not readable, a reason is given on Form 4. If readable, the PET data are registered to the MR and are subjectively reviewed in conjunction with the MR. A representative image transverse image plane through the tumor is selected for review. Uptake in the tumor (as defined by the MR) is subjectively judged on a 5-point scale (FDG less than white matter, FDG uptake similar to white matter, FDG uptake more than white matter but less than gray matter, FDG uptake similar to gray matter, FDG uptake greater than gray matter) The uniformity of the uptake is judged to be 0-25%, 26-50%, 51-75% or 76-100% of the tumor as defined by MR. It is also determined whether the FDG uptake correlates with regions of MRI contrast enhancement. This subjective analysis is followed by quantitative, region of interest (ROI) analyses. On the

representative transverse plane selected above, 4 ROIs are drawn: one around the tumor, one in comparable gray matter, one in comparable white matter and one about the entire brain. If the tumor is not in a transverse slice that contains comparable gray and white matter, a second transverse plane is selected for the comparison ROIs. The mean and maximum pixel values within each of the ROIs are recorded. Ratios of tumor/gray matter, tumor/white matter and tumor/whole brain using both mean and maximum pixel counts are determined.

3D Image Analysis

In selected cases 3D image analysis has been done. 3D Image Analysis Tumor volumes of interest (VOIs) are defined on both FLAIR and T1 post-contrast (PC) MR images. The areas defined are the areas of hyperintense signal on the FLAIR images and enhancing tumor on the T1 post-contrast MR images. After volumes of interest are manually drawn on the MR images, they are confirmed by a nuclear medicine physicist and pediatric neuroradiologist and transferred to the co-registered PET images. Four 3D FDG uptake metrics have been determined for each PET VOI. The mean pixel value within the VOI is determined and this value is normalized by the mean value within the comparison VOI of either normal gray or white matter yielding the Tumor Gray Matter Ratio (Mean) and Tumor White Matter Ratio (Mean) values, respectively. The Tumor Gray Matter Ratio (Maximum) and Tumor White Matter ratio (Maximum) is defined similarly except the maximum pixel value within the VOI is used instead of the mean. For the Tumor Gray matter Ratio (Total) and the Tumor White Matter Ratio (Total), all of the pixel values within the VOI are added yielding a cumulative metric, and this value is normalized by a similar value for the gray or matter comparison VOI, respectively. The inhomogeneity index is defined as the ratio of the standard deviation of the pixel values within the VOI normalized by the mean.