Pediatric Brain Tumor Consortium
Neuroimaging Center

Boston Children's Hospital
Department of Radiology

Manual of Operations

Pediatric Brain Tumor Consortium Members

Temporary Participating Member Institutions:

Children's Hospital of Philadelphia, Seattle Children's Hospital, and University of California San Francisco

Pediatric Brain Tumor Consortium Neuroimaging Center

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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 Clinical Research Center 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

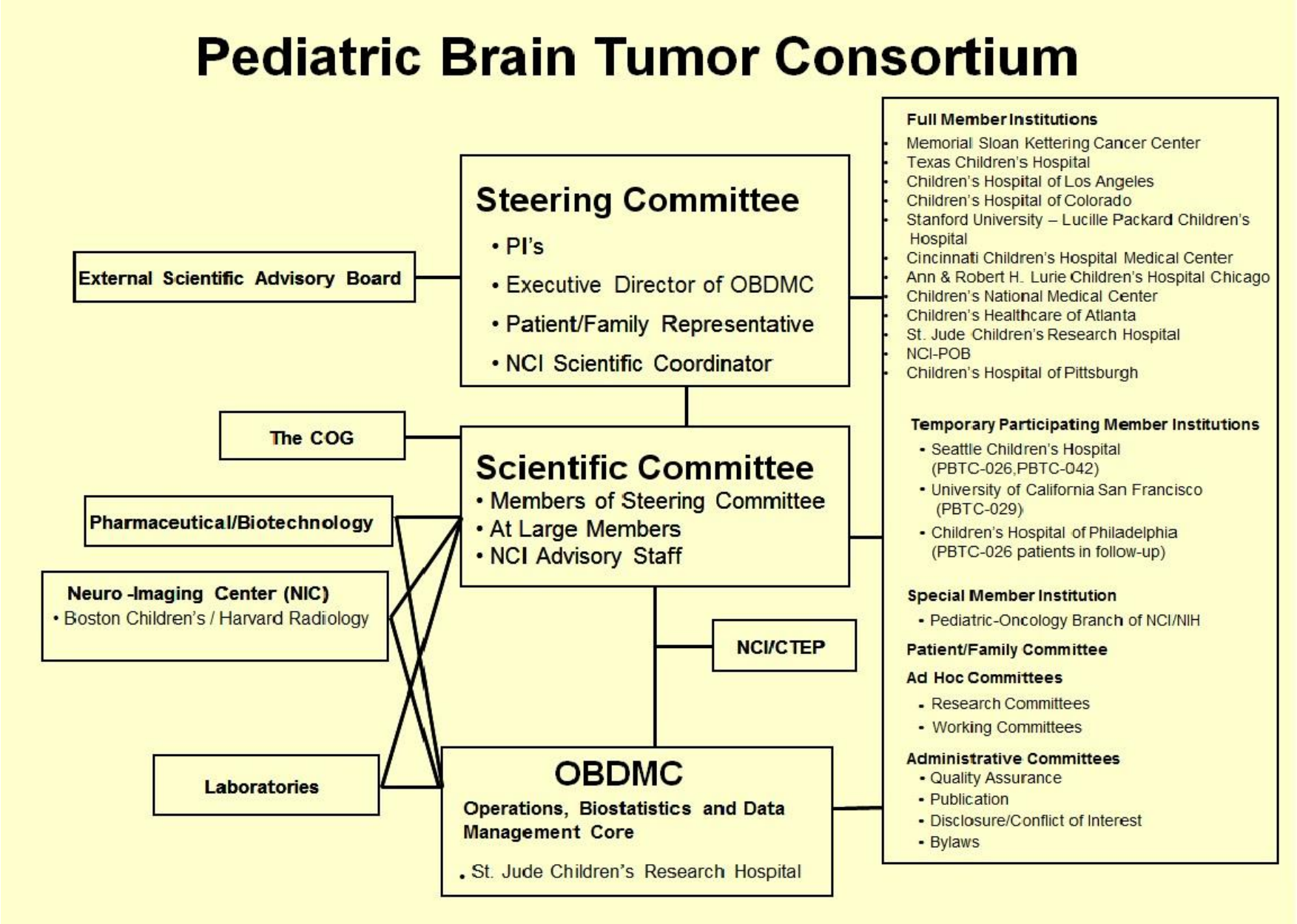

Table 1: PBTC NIC MR Equipment List

Site Code	Institution	Contact Name	Personnel	Contact Telephone	Contact Email
11	Children's National Medical Center Washington, DC	Vezina, Gilbert, MD Holder, Anne	MR Physician MR Technologist	202-476-2389 202-884-2969	gvezina@cnmc.org aholder@cnmc.org
13	Duke University Medical Center Durham, NC	Lascola, Christopher, MD Hinton, Joseph	MR Physician MR Technologist	919-684-7218 919-684-7254	christopher.lascola@duke.edu joseph.hinton@duke.edu
14	Boston Children's Hospital Boston, MA	Mulkern, Robert, PhD Biagiotti, Diane	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	Panigrahy, Ashok, MD Willaman, Dennis	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	Patay, Zoltan, MD Herring, Kendri Brady, Samuel	MR Physician MR Technologist MR Technologist (QA)	901-595-2718 901-595-2013 901-595-8728	zoltan.patay@stjude.org kendri.herring@stjude.org samuel.brady@stjusde.org
18	Texas Children's Hospital at Baylor Houston, TX	Jones, Jeremy, MD Dowdy, Dionne	MR Physician MR Technologist	832-822-5234 832-824-6330	jyjones@texaschildrens.org drdowdy@texaschildrens.org
20	National Institutes of Health Bethesda, MD	Patronas, Nicholas, MD Evers, Robert	MR Physician MR Technologist	301-402-5726 301-402-5586	npatronas@cc.nih.gov robert.evers@nih.gov
21	Lurie Children's Hospital of Chicago Chicago, IL	Marci Messina	MR Supervisior	312-277-3470	mmessina@luriechildrens.org
22	Cincinnati Children's Hospital Medical Center Cincinnati, OH	Jones, Blaise, MD Young, Julie	MR Physician MR Technologist	513-636-7475 513-636-5805	blaise.jones@cchmc.org julie.young@cchmc.org
23	Children's Hospital Los Angeles Los Angeles, CA	Nelson, Marvin, MD Kohatsu, Arthur	MR Physician MR Technologist	323-361-2411 323-361-2411	mdnelson@chla.usc.edu akohatsu@chla.usc.edu
24	Memorial Sloan-Kettering Cancer Center New York, NY	Haque, Sofia, MD Mair, Thomas	MR Physician MR Technologist	212-639-7170 212-639-6342	haques@mskcc.org mairt@mskcc.org
25	Lucile Packard Children's Hospital at Stanford Palo Alto, CA	Yeom, Kristen, MD Karen Roldan	MR Physician MR Technologist	650-721-2388 (650) 724-2676	kyeom@stanford.edu KRoldan@stanfordchildrens.org
27	Children's Hospital of Colorado Aurora, CO	Nicholas Stence, MD Misty King	MR Physician MR Technologist	720-777-8571 720-777-8571	Nicholas.Stence@ucdenver.edu misty.king@childrenscolorado.org
28	Children's Healthcare of Atlanta Atlanta, GA	Susan Palasis, MD Melissa Weisel Trista Raymer	MR Physician MR Technologist Egleston MR Technologist Scot Rite	404-785-2055 404-785-6650	susan.palasis@choa.org Melissa.weisel@choa.org Trista.raymer@choa.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)	24.0 25.0 24.0	Gadavist 0.1 ml/Kg Dotarem 0.2 ml/Kg
13	Duke University Medical Center Durham, NC	Siemens 3T Skyra (2) Siemens 3T TimTrio (1) Siemens 1.5T Aera (2) Siemens 1.5T Avanto (2) GE 1.5T 450w (2) GE 1.5T Signa HDXT (1)	D13 B19 D13 B17 DV25 V15	Multihance 0.2ml/kg Prohance 0.2ml/kg
14	Boston Children's Hospital Boston, MA	GE 1.5T (1) Siemens 3T (4) Siemens 1.5 (1)	15.0 VB17 VB17	Gadavist 0.1 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	All magnets on E11C level.	Gadavist 0.1 ml/kg 10 ml max.
18	Texas Children's Hospital at Baylor Houston, TX	Philips Achieva (1.5T) Philips Ingenia (1.5T) Philips Ingenuity (3.0T) Siemens Skyra (3.0T) Siemens Vida (3.0T)	Manufacturer supplied software	Gadavist 0.1 ml/Kg Dotarem 0.2 ml/Kg?
20	National Institutes of Health Bethesda, MD	Siemens VERIO 3.0T Philips Tx Achieva 3.0 T Siemens mMR 3.0 T Siemens Aera 1.5 T (2)	VB17 R5 3.2.3.1 vb20 VD13	Magnavist 0.2 ml/Kg Multihance 0.2 ml/kg Prohance 0.2 ml/Kg Gadavist 0.1 ml/Kg
21	Lurie Children's Hospital of Chicago Chicago, IL	Siemens Aera (2) 1.5T Siemens Skyra (1) 3T GE Signa HDxt(1) 1.5T	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 1.5T (3) GE 3T (2) Philips 1.5T (4) Philips 3T (1)	S/W ver. HD23 s/w ver. 5.3 s/w ver. DV26 s/w ver. 5.3	Dotarem 0.2 ml/Kg Eovist 0.2ml/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
24	Memorial Sloan-Kettering Cancer Center New York, NY	GE Signa** 750W GE Signa*** 1.5T GE 450W 450W GE 750 3T	GE Signa 750W DV25 GE Signa 1.5T V12 GE 450W DV24 GE 750 3T DV24 V24 & V25	Gadavist 0.1 ml/Kg

Table 1a: PBTC NIC MR Equipment List

Site Code	Institution	Equipment Vendor/Model*	Software Version	Contrast
25	Lucile Packard Children's Hospital at Stanford Palo Alto, CA	GE, MR5 (CHMR5), intra OP MRI, 750w 3T; GE, MR6 (CHMR6) PET MRI.	NEW: MR5-DV26.0_1810b & MR6-MP26.0_1747c OLD: MR2-DV26.0_1725a; MR1-DV26.0_1725a; MR3-DV26.0_1725a	Multihance 0.2 ml/Kg Gadavist 0.1 ml/Kg
27	Children's Hospital of Colorado Aurora, CO	Philips Ingenia 3T (MRI 2) Philips Ingenia 1.5T (MRI 3) Philips Ingenia 3T (MRI 4)	MRI 2 and 4 - 5.3 MRI 3 - 5.3.1	Multihance 0.2 ml/kg
28	Children's Healthcare of Atlanta Atlanta, GA	Egleston: Siemens Tim Trio 3T Aera 1.5T Siemens AvantoFit 1.5T Scottish Rite: Siemens Prisma Fit Philips Ingenia Siemens Avanto Siemens Skyra	Egleston: Trio - B17 Aera - E11A AvantoFit - E11B Scottish Rite: Prisma - VE11B Ingenia - 5.1.3 Avanto - VB19A Skyra - VE11A	Magnevist 0.1 ml/kg Multihance 0.1 ml/kg 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)	Pseudo-continuous 3D ASL; DV26.0 Tumors, neonates, and acute neurologic derangement	Both Yes
13	Duke University Medical Center Durham, NC	Siemens 3T Skyra (2) Siemens 3T TimTrio (1) Siemens 1.5T Aera (2) Siemens 1.5T Avanto (2) GE 1.5T 450w (2) GE 1.5T Signa HDXT (1)	D13 B19 D13 B17 DV25 V15	Multihance 0.2ml/kg Prohance 0.2ml/kg
14	Boston Children's Hospital Boston, MA	Siemens 3T	PASL Tumors, Stroke	Both Yes
15	Children's Hospital Pittsburgh of UPMC Pittsburgh, PA	GE 1.5T (2) GE 3.0T (1)	GE – 3DASL, 1.5T 16, 3T 25 Tumor-Epilepsy-Stroke-Lesion	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	2d Epi Fid on E11C Intracranial steno-occlusive arterial disease	Both No
18	Texas Children's Hospital at Baylor Houston, TX	ASL not acquired	None	None
20	National Institutes of Health Bethesda, MD	ASL not acquired	None	None
21	Lurie Children's Hospital of Chicago Chicago, IL	ASL not acquired	None	None
22	Cincinnati Children's Hospital Medical Center Cincinnati, OH	GE 1.5T (3) GE 3T (2) Philips 1.5T (4) Philips 3T (1)	GE product ASL - 3.0Tand l.5T- HD23 and DV26 2/w ver (30 spiral continuous ASL) Philips product ASL - 3.0T and l.5T- s/w/ ver R5.3 and R5.4- 20 pCASL EPI	Both Routine – No Optional - Yes
23	Children's Hospital Los Angeles Los Angeles, CA	Philips (3.0T)	Phillips 5.3 pCASL	Research Routine – No Optional - Yes
24	Memorial Sloan-Kettering Cancer Center New York, NY	ASL not acquired	None	None
25	Lucile Packard Children's Hospital at Stanford Palo Alto, CA	MR1-1.5T; MR2-3T; MR3-3T; MR5-3T; MR6-3T	3D ASL (NON CONTRAST), FAST SPIRAL. MP26.0_1747c, DV26.0_1725a, DV26.0_1810b	Clinical Yes

Site Code	Institution….. ASL Information	Equipment Vendor/Model* ASL Information	Pulse Sequence Indications	1. Clinical/Research/Both? 2. Routine for Brain Tumors?
27	Children's Hospital of Colorado Aurora, CO	Philips Ingenia 3T (MRI 2) Philips Ingenia 1.5T (MRI 3)	pCASL, 5.3 Suspected stroke, hemip;legic migraine, new tumor	Research Routine – No Optional - Yes
28	Children's Healthcare of Atlanta Atlanta, GA	Egleston: Aera 1.5T Siemens AvantoFit 1.5T Scottish Rite No ASL	Egleston: E11 A and B None	Clinical Routine – No Optional – Yes None

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	Pranav Vyas, MD Stanley Fricke*	PET Physician PET Physicist	202-476-5630 202-476-6153	pvyas@childrensnational.org sfricke@cnmc.org
13	Duke University Medical Center Durham, NC	GE Discovery 690 PET/CT GE Discovery IQ 5-ring PET/CT	James, Olga, MD Turkington, Timothy PhD Hawk, Thomas, BS	PET Physician PET Physicist Computer Specialist	919-684-7647 919-684-7706 919-684-7714	olga.james@dm.duke.edu timothy.turkington@duke.edu thomas.hawk@duke.edu
14	Boston Children's Hospital Boston, MA	Siemens mCT 64 PET/CT	Voss, Stephan, MD Fahey, Fred, DSc* Cao, Xinhua, PhD	PET Physician PET Physicist Computer Specialist	617-355-8317 617-355-2809 617-355-5563	Stephan.voss@childrens.harvard.edu Frederic.fahey@childrens.harvard.edu xinhua.cao@childrens.harvard.edu
15	Children's Hospital Pittsburgh of UPMC Pittsburgh, PA	GE Discovery DVCT PET/CT	Nghi Nguyen, MD N/A Czachowski, Michael, MBA*	PET Physician PET Physicist Nuclear Tech Supervisor	412-692-9518 412-692-9518	nguynennc@upmc.edu Michael.Czachowski@chp.edu
16	St Jude Children's Research Hospital Memphis, TN	GE Discovery 690	Shulkin, Barry, MD, MBA Foster, Nancy Artz, Nathan PhD	PET Physician Computer Specialist PET Physicist	901-595-3347	Barry.shulkin@stjude.org Nancy.foster@stjude.org Nathan.Artz@stjude.org
18	Texas Children's Hospital at Baylor Houston, TX	Philips Vereos Digital PET/CT	Victor Seghers, MD McMullen, Tara Zapien, Veronica	PET Physician PET Technologist Admin. Asst.	832-826-8525 832-826-8578 832-826-8525	vjsegher@texaschildrens.org tlmcmull@texaschildrens.org vszapien@texaschildrens.org
20	National Institutes of Health Bethesda, MD	Siemens MCT PET/CT (2)	Herscovitch, Peter, MD Barker, Craig, PhD Fraser, Charles	PET Physician PET Physicist Computer Specialist	301-451-4248 301-451-3558 301-451-3591	pherscovitch@cc.nih.gov cbarker@cc.nih.gov cfraser@cc.nih.gov
21	Lurie Children's Hospital of Chicago Chicago, IL	GE PET/CT Discovery 690 12123PT6	Paige Nelson Quijano, Carla, MD Delilah Burrowes, MD Christina Sammet, PhD	Research Coordinator PET Physician PET Physician PET Physicist	312-2273479 312-227-4500 312-227-4388 312-227-3393	pnelson@luriechildrens.org cquijano@luriechildrens.org dburrowes@luriechildrens.org csammet@luriechildrens.org
22	Cincinnati Children's Hospital Medical Center Cincinnati, OH	Philips Ingenuity TF	Andrew Trout, MD Susan E. Sharp, MD (backup) Samuel Brady Jay Moskovitz (information tech) Leonid Rozhkov (analytic methods)	PET Physician PET Physician PET Physicist Computer Specialist Computer Specialist	513-803-3004 513-636-6662 513-800-4516 513-636-5981 513-803-0545	andrew.trout@cchmc.org Susan.sharp@cchmc.org Samuel.brady@cchmc.org Jay.moskovitz@cchmc.org Leonid.rozhkov@cchmc.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
24	Memorial Sloan-Kettering Cancer Center New York, NY	General Electric PET/CT	Neeta Pandit-Taskar, MD Ross Schmidtlein Brad Beattie John Humm Hovanes Kalaigian Shawn Davie	PET Physician PET Physicist PET Physicist PET Physicist PET Physicist MITS Manager	212-639-7372 212-639-8082 646-888-2579 212-639-7367 212-639-7382 212-639-7375	Pandit-n@mskcc.org schmidtr@mskcc.org beattieb@mskcc.org hummj@mskcc.org kalaigih@mskcc.org davies@mskcc.org

25	Lucile Packard Children's Hospital at Stanford Palo Alto, CA	GE DMI	Andrei Iagaru, MD Craig Levin, PhD	PET Physician PET Physicist	650-725-8263 650-736-7211	aiagaru@stanford.edu cslevin@standord.edu
27	Children's Hospital of Colorado Aurora, CO	Siemens Biograph 40	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 40 Model# 10097304	Adina Alazraki, MD Cassandra Dike, PET Supervisor	PET Physician PET Supervisor	404-785-0474	alazraki@choa.org Cassandra.dike@choa.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
13	Duke University Medical Center Durham, NC	F18-FDG,F18-FLT, F18-fluorbetapir	GE AW MIMVista Linux WS	Radiolabeled mab therapy for brain tumors - PET f/u, Metabolic effects of radiation therapy on cognitive function (FDG), dementia, plaque imaging compounds for dementia , FLT
14	Boston Children's Hospital Boston, MA	FDG, FLT	Hermes Medical Solution Workstation	Animal Micro PET, Epilepsy-spect
	Dana Farber Cancer Institute Boston, MA	FDG, FLT (pending)	ECAT Software (CTI), Xeleris/AW (GE), Hermes, Siemens Leonardo/True D	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 MIMVISTA SOFTWARE Neuro Package	Possible FLT in near future also, Amyloid Imaging
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, H20, fdopa, fcway, flumazenil, nnc, leucine, dasb, fallypride, raclopride, methylreboxitine, DTBZ, FP-TZTP, FCWAY, arachidonic acid, docosahexaenoic acid, acetate Ga-68 DOTATATE	Siemens mCT (x2) PACS	epilepsy, Alzheimer's, Parkinson's, schizophrenia, depression, obsessive compulsive disorder, tumor, alcohol abuse, movement disorders, Fragile X, TBI
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 (2,3), Tc-99m-ECD (2,3), Tc-99m-HMPAO (2,3), (2) used for clinical studies, (3) available locally	Analyze 10, SPM, Brain Lab, MIM Neuro	Epileptogenic focus localization

		* (1)=Available in co-operation with Kettering Medical Center, Dayton, OH. (2)=Used for clinical studies. (3)=Available locally. (4)=Used for human research studies only. (5)=Only used for non-human experiments to date. (6)=Will require patient transportation to off campus site.		
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	GE PET VCAR Hermes Medical Systems	F-choline in brain protocol is with pediatric neuro-oncology group IRB # 14-275 PI at MSKCC- Neeta Pandit-Taskar Co PI: Ira Dunkel; Kim Kramer
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 Siemens Leonardo workstation	For PET, none
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	None at present.

Table 3: PBTC Institutions and Principal Investigators

CHILDREN'S NATIONAL MEDICAL CENTER	TEXAS CHILDREN'S CANCER CENTER / BAYLOR
Roger Packer, M.D. & Brian Rood, M.D. **Children's National Medical Center** Department of Neurology 111 Michigan Avenue, NW Washington, DC 20010 TEL: 202/884-2120 FAX: 202/884-5226 E-MAIL: rpacker@childrensnational.org & brood@childrensnational.org SITE 11	**Murali Chintagumpala, M.D. & Patricia Baxter, M.D.** **Texas Children's Cancer Center** 6621 Fannin Street, MC 3-3320 Houston, Texas 77030 TEL: 800/CANCER9 FAX: 832/825-4299 E-MAIL: mxchinta@txccc.org ; pabaxter@txch.org SITE 18
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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, particularly in antiangiogenesis protocols. 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 suscepitiblity 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 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 is done particularly in antiangiogenesis protocols with 3D axial T1 dynamic contrast enhanced sequences which with kinetic modeling yield 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 (Ktrans),

fractional blood-plasma volume (Vp), and the volume of the extravascular extracellular space per unit volume tissue (Ve)

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	Stratum 1: Patients not on enzyme-inducing anticonvulsant drugs Stratum 2: 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	Stratum 1: patients previously not treated with RT or only focal RT Stratum 2: patients with prior craniospinal irradiation or myeloblative 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	Stratum 1: newly diagnosed localized brainstem tumors Stratum 2A: recurrent intracranial malignant gliomas - not using EIACD Stratum 2B: 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	Stratum 1: Newly diagnosed intrinsic brain stem glioma or incompletely resected supratentorial malignant gliomas not receiving enzyme-inducing anti-convulsant drugs Stratum 2: 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	Stratum IA: medulloblastoma patients with measurable disease Stratum IB: medulloblastoma patients with only positive CSF cytology or with linear leptomeningeal disease; Stratum II***:*** will include patients with supratentorial primitive neuroectodermal tumor (S-PNET) including pineoblastomas, and ependymoblastomas; Stratum III***:*** 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)- 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 06-Benzylguanine and Temozolomide in Pediatric Patients with Recurrent or Progressive High-Grad Gliomas and Recurrent or Progressive Brainstem Tumors	Stratification Patients will be stratified according to tumor type: Stratum A Recurrent or progressive high grade gliomas Stratum B 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: Stratum 1: those who are not receiving steroids; Stratum 2: 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	Stratum 1: no prior XRT or focal XRT only and/or < 2 prior myelosupressive chemotherapy regimens; Stratum 2: prior craniospinal XRT, high-dose chemotherapy, and/or > 2 prior myelosupressive 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	Stratum 1: Those who are not receiving enzyme inducing anticonvulsant drugs (EIACD) Stratum 2: 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	Stratum A: Recurrent, progressive or refractory high-grade gliomas Stratum B: Recurrent, progressive or refractory Intrinsic brain stem tumors Stratum C: Recurrent or progressive Medulloblastomas Stratum D: Recurrent or progressive Ependymomas Stratum E: Recurrent low grade gliomas	Study completed	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. 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). 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
PBTC-023	Phase I and Pharmacokinetic Study of Enzastaurin (LY317615) in Children and Adolescents with Refractory Primary CNS Tumors	No strata	Study completed	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. 1. Results of imaging studies will be combined across similar PBTC protocols to increase the power for detecting correlations among scans and with outcome.
PBTC-024	A Phase I Study of MK-0752 in Pediatric Patients with Recurrent or Refractory CNS Malignancies	No strata	Study completed	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.
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	Open to accrual	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	Stratum 1: 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. Stratum 2: 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. Stratum 3: Patients with NF-1 associated progressive, recurrent or refractory low grade glioma (WHO I or II), with or without tissue Stratum 4: Patients with non-NF1 associated progressive, recurrent or refractory optic pathway glioma (OPG) with or without tissue available for BRAF evaluation. Stratum 5: Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than pilocytic astrocytoma or optic pathway	Open	To describe MRI characteristics of the tumors before and after treatment to determine if there is an early diffusion indicator of response.

		glioma) with a BRAF aberration. Stratum 6: Patients with non NF-1 associated progressive, recurrent or refractory low grade glioma (other than OPG) with tissue available for BRAFanalysis who cannot be classified into Stratum 1, 2 or 5 due to inadegquate tissue quality		
PBTC-029C - Retreatment	A Phase 1 and Phase II Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma	No strata	Open	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	Strata A: Patients without evidence of activation of Hedgehog signaling pathway Strata B: 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	Open	To explore the quantitative MR measures of relative cerebral blood volume (rCBV), vascular permeability (Ktrans, vp, and ve 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	Open	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	Stratum 1: 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 Stratum 2: Patients with progressive or recurrent craniopharyngiomas following radiation therapy.	Open	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	Stratum A: DIPGs Stratum B: non-brainstem HGGs	Open	No correlative objective MR for response only

PBTC-043	A Phase I Trial of Pomalidomide for children with recurrent, progressive or refractory CNS tumors	Stratum 1: Patients on or off steroids Stratum 2: Patients on steroid, <12 Years Old Stratum 3: Patients off steroid, <12 Years Old Stratum 4: Patients on steroid, >=12 Years Old Stratum 5: Patients off steroid, >=12 Years Old	Open	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.	Stratum A: patients with progressive, recurrent or refractory DIPGs Stratum B: patients with progressive, recurrent or refractory non-brainstem HGGs.	Open	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 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
PBTC-047	A Phase I Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma	No Strata	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	No Strata	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	No Strata	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	No Strata	Open	No correlative response. MR for response only.

Table 7: PBTC Protocols [001 – 013]

Protocol	Trial	MR Brain	MR Diffusion	MR Perfusion	MR Spectro-scopy	Cister-nogram	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 SpartajectTM-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)-a 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	Cister-nogram	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	+	+							

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	**+**					**+**			

* DTI
** MR of knee required

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 Sinead Christensen at the Clinical Research Center 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 Clinical Research Center 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 CRC 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 CRC 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
858 794-7200

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 $\pm$ 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

Slice thickness = 0.2 x (63 x 41/(63 + 41)) = 4.97 mm

Which is well within the specified range of 5.0 $\pm$ 0.7 mm required for acceptance.

Test 4: Slice Position Accuracy

Slices 1 and 11 are aligned with the vertices of crossed 45º 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 mm^2 area) was selected and two regions-of-interest (ROI's), 100 mm^2 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

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

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

$$\text{Ghosting ratio} = (\text{left} + \text{right} - \text{top} - \text{bottom})/(2 \times ROI_{large})$$

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. The NIC Research Coordinator, Sinead Christensen, 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 CRC. The data forms are entered directly through the PBTC web-based data management system and managed by the PBTC Operations and Biostatistics Center. All other data such as quality assurance data are entered into an SPSS database at the CRC. For these data, the CRC generates data entry status reports and generates frequency distributions of study variables to provide timely and relevant feedback to the NIC. A password protected study directory is established on the program's server for all database files and analysis files. Datasets are cleaned, verified, archived with documentation and then used to create documented analysis files. Access to programs and datasets is denied by password to non-study staff. 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 Clinical Research Center. 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 > 230 academic/non-profit consortium partners on six continents and 24,000 research end-users (www.project-redcap.org)

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

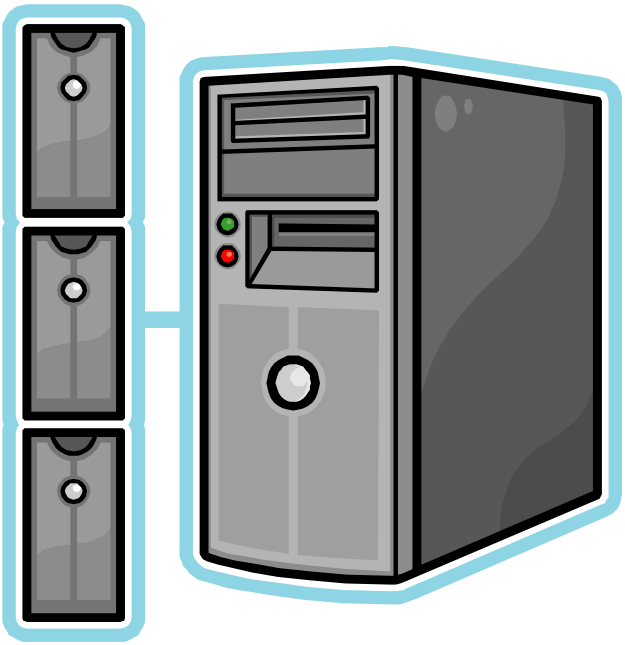
Clinical Data Management System

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)

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

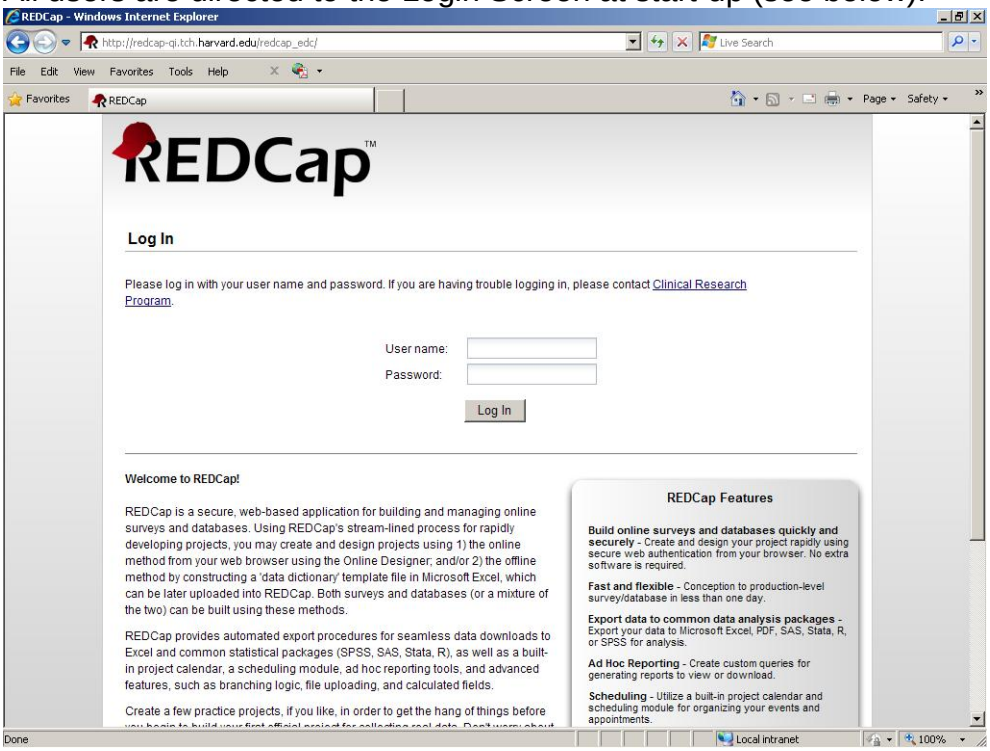
As stated previously, the DMS is a Web-based system accessible from inside the Boston Children's Hospital, intranet only. The Web site requires users to employ Internet Explorer version 8 or higher.
The data management system is accessible through the following URL.
http://redcap-qi.tch.harvard.edu/redcap_edc/

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

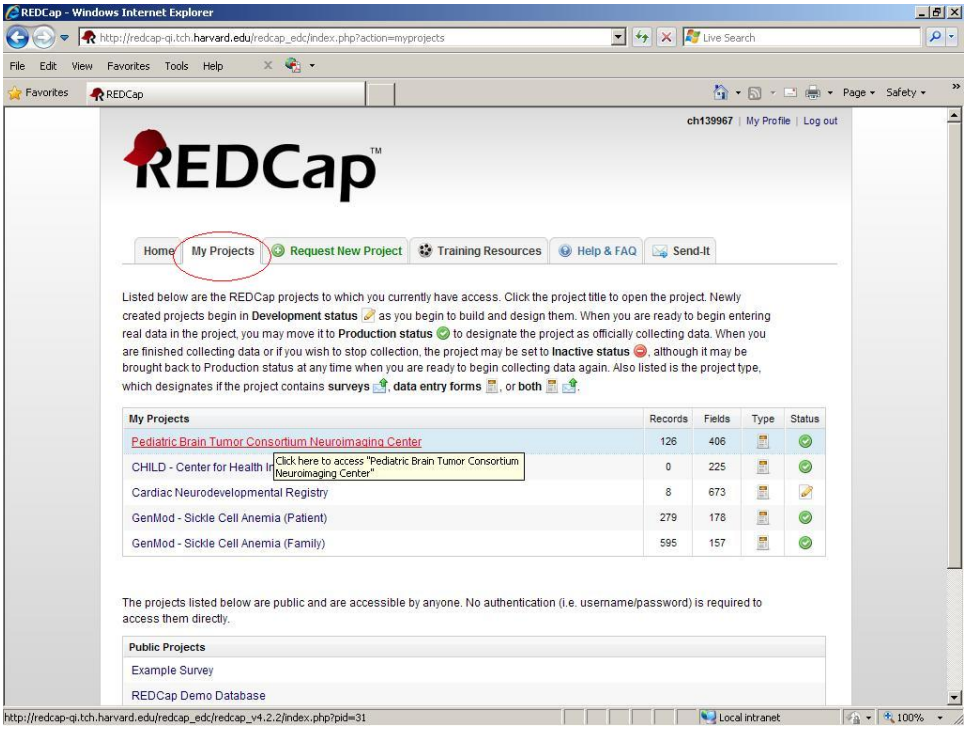
All users are directed to the Login Screen at start-up (see below).



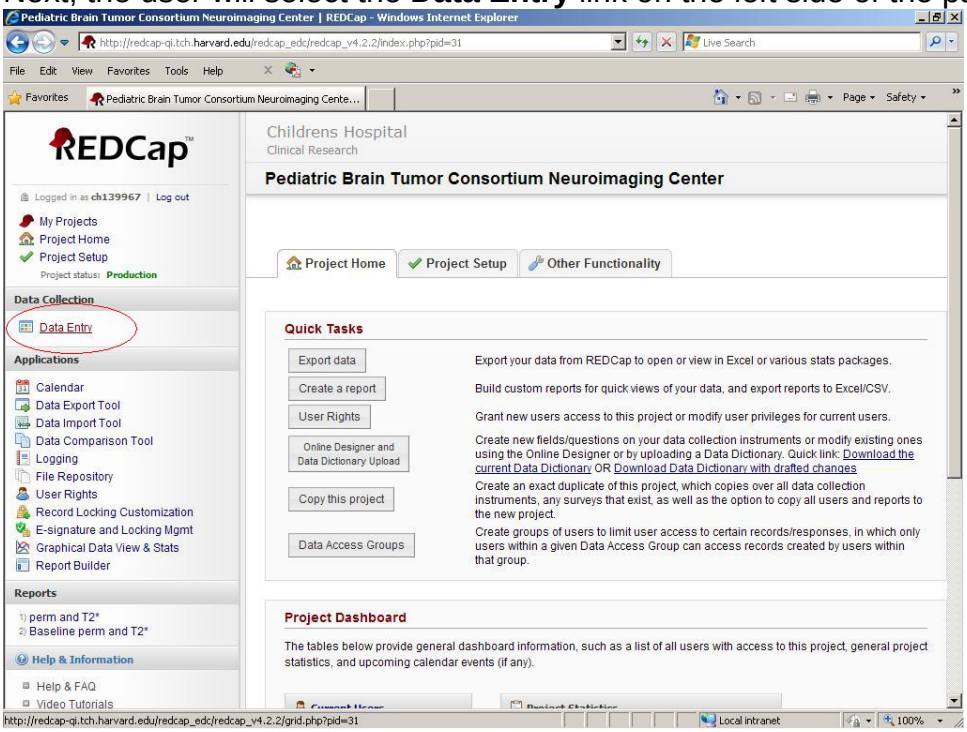
If a user has difficulty logging in, they may select the Clinical Research Center link and request help.

Home (Portal) Screen

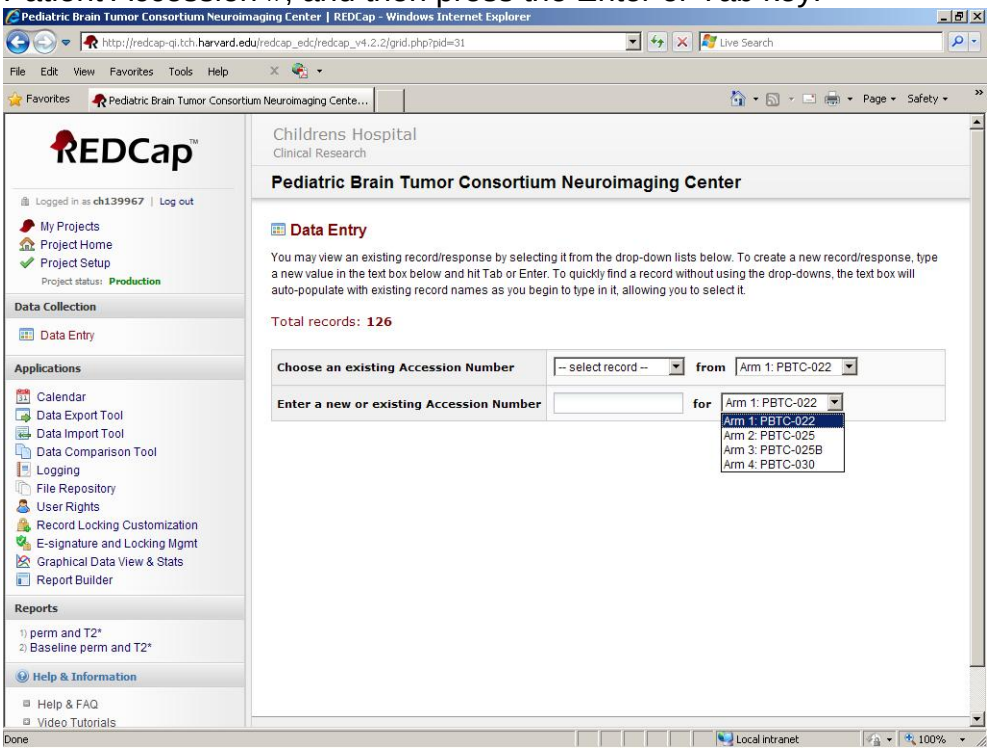
Upon logging in, the user must select the **My Projects** tab. From there, the user will click on the link labeled **Pediatric Brain Tumor Consortium Neuroimaging Center**.



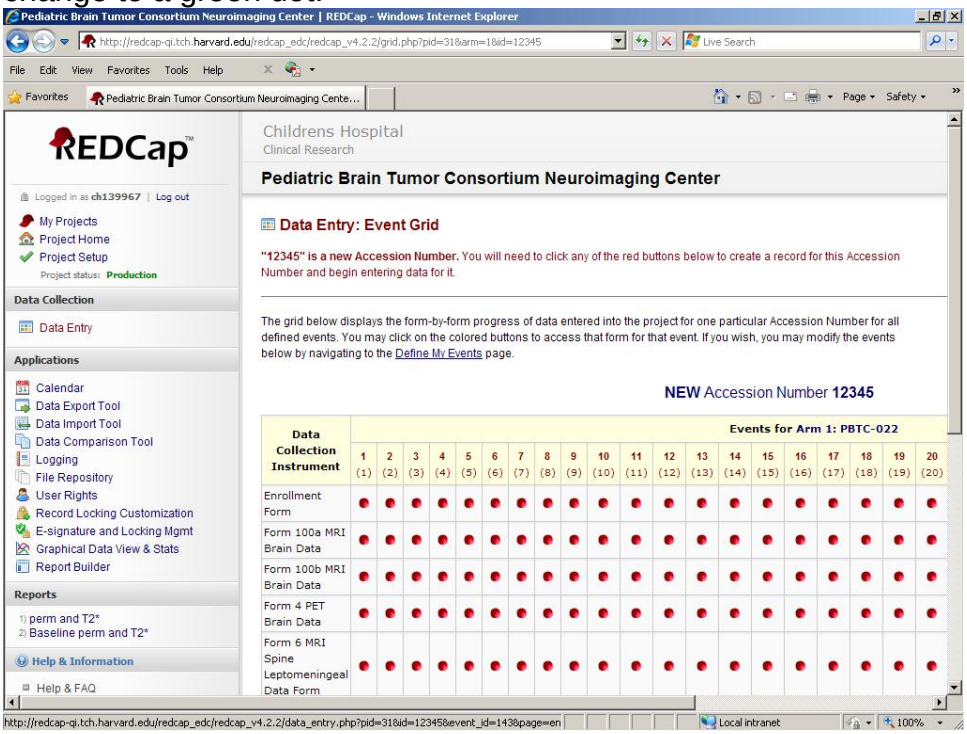
Next, the user will select the **Data Entry** link on the left side of the page.



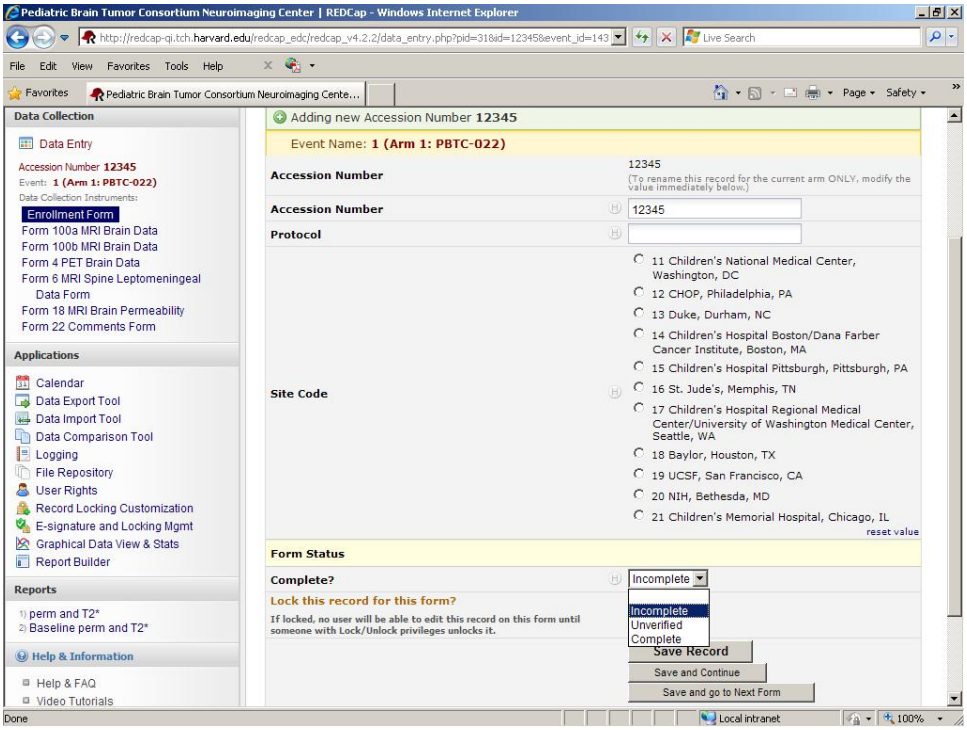
On the next screen, the user must select the arm (or PBTC Protocol), enter the Patient Accession #, and then press the Enter or Tab key.



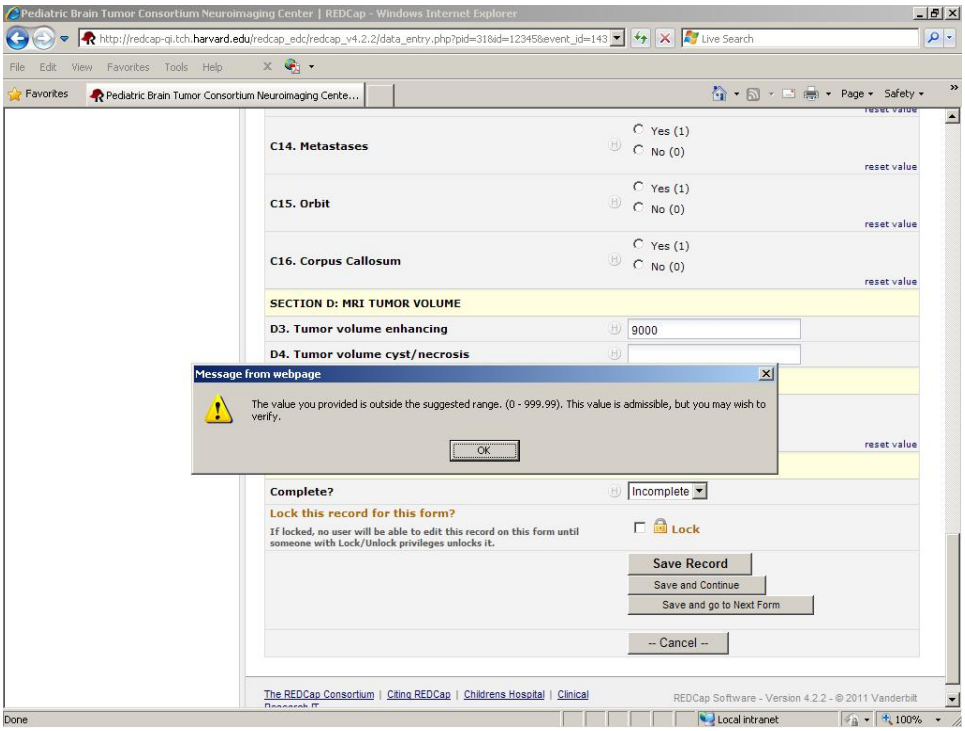
Next, the user must select the appropriate **Data Collection Instrument** (or Form) and **Event** Number for data entry. Red dots designate forms that have not been entered yet. Once a form has been entered and saved, the red dot will change to a green dot.



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. The user will have the opportunity to accept or re-enter the out-of-range value.



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 from at the OBC. 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 OBC, 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 µCi/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 68Ge/68Ga 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).

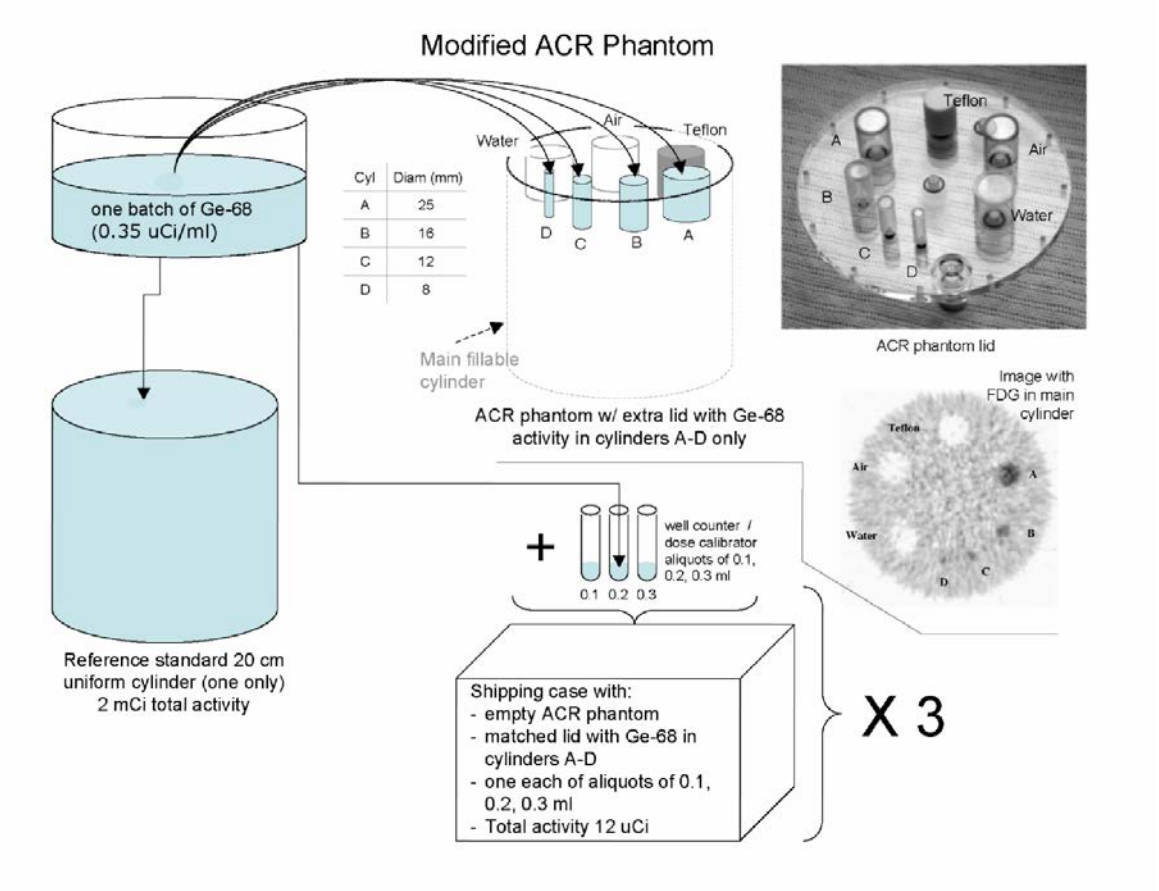


*Image courtesy of University of Washington – Seattle

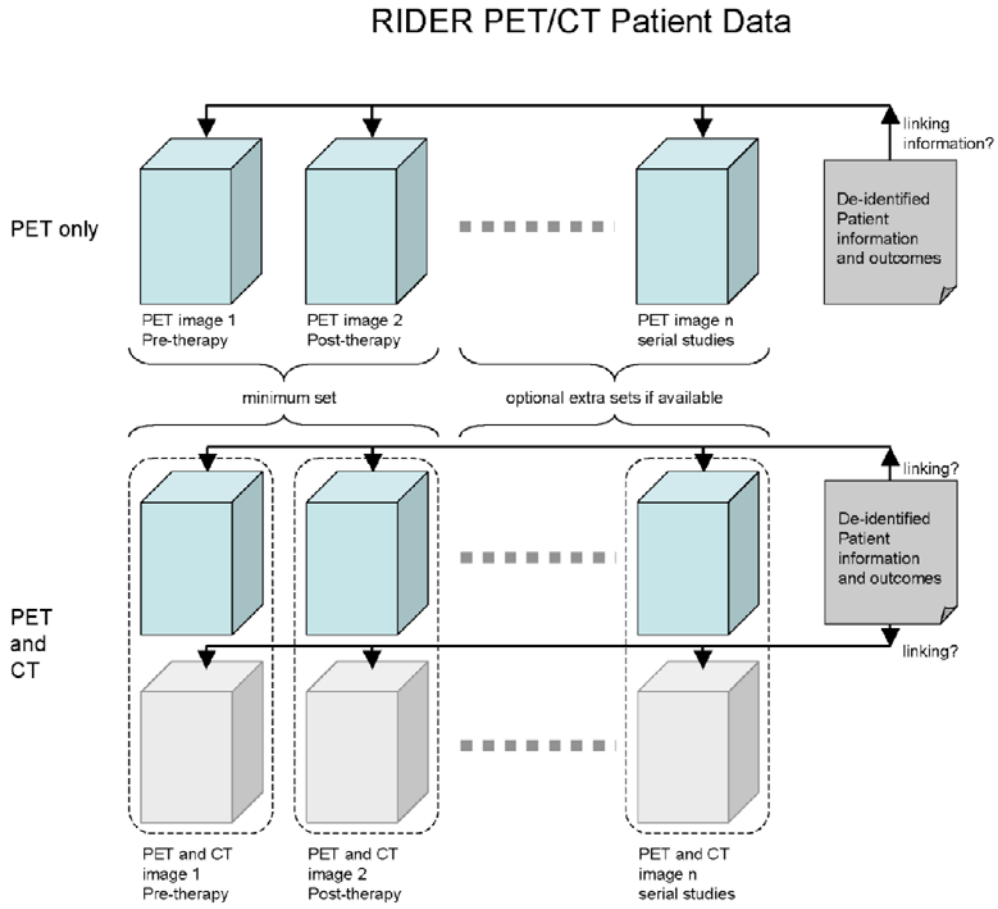


*Image courtesy of University of Washington – Seattle

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.