INTERNATIONAL DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG) REGISTRY AND REPOSITORY

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ABSTRACT

There are limited data regarding the biology of diffuse intrinsic pontine gliomas (DIPG). This project provides the infrastructure for acquisition of biological specimens, imaging, and correlative clinical data to facilitate biology studies in this group of patients. This registry will collect clinical, demographic, radiological and pathological data and specimens (if available) from patients with DIPG, both prospectively (in newly diagnosed or currently living patients), as well as retrospectively (in patients who are deceased). Cases are identified through:

1. Existing clinical and/or cancer registry databases
2. Referrals from clinicians, surgeons, or pathologists
3. Families initiating contact with Registry staff directly

The following data/materials will be collected:

**Clinical:** Demographic data, date of diagnosis, signs and symptoms at diagnosis, laboratory data, detailed treatment data (e.g. types and dates of surgeries (if any), chemotherapy, radiotherapy), best response to treatment, dates of progression, types of progression (local or metastatic), and follow-up data. The demographic and clinical data collected are abstracted and entered into an electronic data system secured by password protection (see section 4.2). Each patient in the data system is given a unique Registry number.

**Imaging:** All radiographic imaging obtained since diagnosis will be requested at the time of study entry. All images submitted to the DIPG Registry will be deidentified, uploaded and stored in the research Amicas® PACS system housed at CCHMC. A panel of study neuroradiologists will review all of the images submitted. The radiographic images will be stored indefinitely in the research PACS system with the patient’s assigned Registry number alone. Common data elements will be abstracted from the imaging and stored in the Registry electronic data system.

**Pathology Central Review:** If glass slides (stained or unstained) or paraffin blocks of tumor tissue (from biopsy or autopsy) are available, they will be requested at the time of registry entry but are not mandatory for enrollment. Pathology slides will be digitized at CCHMC and the resulting images will be reviewed by a panel of neuropathologists for independent confirmation of diagnosis. Digital images of the slides will be stored in the Division of Pathology and Laboratory Medicine at CCHMC. After digitization at CCHMC, pathology materials will be identified and stored by the patient’s assigned Registry number in the DIPG Tissue Repository, as described in section 4.5. Any molecular or immunohistochemical stains that are routinely performed as part of the histopathological evaluation will also be centrally reviewed and may be stored in the electronic data system secured by password protection (see section 4.2). Molecular data will be stored by the patient’s assigned Registry number.

**Bioinformatics repository:** Collection of existing molecular and/or genomic data or analysis that has been performed as well as prospective analysis of tissue from the registry will be submitted to a central bioinformatics repository and may be linked to clinical data housed in the DIPG registry.

**Tissue Collection and Storage for Future Research:** If available, participants’ frozen tissue may be submitted for banking and future research. The tissue will be stored in the DIPG Tissue Repository. This repository will include storage locations at CCHMC, The Hospital For Sick Children, in Toronto Canada, and Sydney Children’s Hospital in Sydney Australia as described in section 4.5.1 and section 4.6.

Data stored in the Registry may be used to provide statistical data for scientific presentations and for preparation of peer-reviewed manuscripts. No personal data can be traced to the study manuscripts.
or presentations. Data and specimens will be released for research proposals upon approval from the International DIPG Registry Committee (see sections 6 and 7, and Appendix I).

The International DIPG Registry and Repository is not associated with any oncology group cooperative study or treatment trial.
1.0 GOALS AND OBJECTIVES

Primary Aims

1.1. To recruit and enroll patients diagnosed with DIPG in the International DIPG Registry and Repository
1.2. To provide a warehouse of clinical, radiological, pathological and demographic data and specimens from patients with DIPG
1.3. To learn more about the biology of DIPG through molecular studies conducted on available tissue samples
1.4. To correlate registry data to a bioinformatics repository of molecular data on DIPG
1.5. To establish collaborations amongst investigators to allow timely data and/or specimen dissemination for future research studies and to develop classification systems, uniform standards of diagnosis, assessment and response, ultimately leading to the development of effective therapies for children with DIPG

2.0 BACKGROUND

Brainstem gliomas account for up to 20% of all CNS tumors in children less than 15 years of age with a median age at presentation of 6-7 years.1 Diffuse intrinsic brainstem gliomas comprise 80% of all brainstem gliomas and are typically Anaplastic Astrocytoma (AA), Glioblastoma multiforme (GBM) or grade 2 lesions. In the United States, 100-150 children develop pontine gliomas per year.2 Prognosis for patients with diffuse intrinsic brainstem gliomas is poor with a median survival of less than one year1,2; fewer than 20% of children are alive at two years. Standard therapy consists of conventional local field radiotherapy to a dose of 54-60 Gy for 6 weeks. Without radiotherapy, median survival is approximately 20 weeks.1,3 Radiotherapy (RT) leads to improved neurological function for a few months and improves overall survival by approximately 2-3 months. Studies that have explored the efficacy of increasing the dose of RT beyond 60 Gy with the use of hyperfractionation using total doses of up to 78 Gy delivered twice daily in smaller dose fractions have demonstrated no significant improvement in survival with 2 year progression free survival of less than 20%.4

No trials have ever shown benefit from using chemotherapy for management of patients with diffuse intrinsic pontine glioma (DIPG). The Children’s Cancer Study Group (CCG) conducted a trial between 1977-1980 to assess the potential benefit of adding chemotherapy to irradiation for children with newly diagnosed brainstem gliomas. Patients were randomized to receive either involved field radiotherapy or irradiation with concomitant vincristine followed by cycles of prednisone, CCNU and vincristine. No difference between the two arms was observed and 5 year survival was about 20%.5 Study CCG 9941 randomized between pre-irradiation use of cyclophosphamide and cisplatin vs ifosfamide and carboplatin. Both regimens led to few objective responses and high progression rates prior to irradiation with no improvement in overall survival. The Pediatric Oncology Group (POG) study POG 8833 showed no benefit from the use of pre-irradiation chemotherapy followed by hyperfractionated irradiation at 6600 cGy.6 Korones et al reported the results of study POG 9836 study using a combination of irradiation at 54 Gy with two 28 day cycles of vincristine and oral etoposide starting concurrently with irradiation and continuing for ten cycles post irradiation. Of the 30 eligible patients, overall survival at one year was 27% ±7% and at 2 years was 3% ±2%. The median survival was 9 months (range 3-36 months). Hematological toxicity was significant.4 Several other studies have similarly demonstrated no survival benefit for patients with DIPG. Marrow ablative chemotherapy (consisting of thiotepa and busulfan, thiotepa and etoposide with BCNU or
carboplatin, or thiotepa and cyclophosphamide) did not demonstrate any survival advantage over radiotherapy alone. 7,8,9

Most recently, the Children’s Oncology Group (COG) and the Pediatric Brain Tumor Consortium (PBTC) have evaluated the efficacy of a variety of radiosensitizing agents (including gadolinium texaphyrin) and biologic agents (including farnesyl transferase inhibitors and epidermal growth factor antagonists). 10,11,12 Novel therapies are clearly needed to treat patients with this devastating disease.

In the US and Canada, the role of surgery has been limited to biopsy in cases where the diagnosis of DIPG is questionable and other histologies (low grade gliomas, PNETs or ependymoma) have been considered based on imaging characteristics of the tumor. Although these tumors are not resectable, the morbidity and mortality rates that have been previously reported have led to a general reluctance to biopsy these lesions unless there is a specific question regarding the diagnosis. More recent studies from Europe, however, have questioned the wisdom of this approach and have advocated biopsy using more modern techniques (such as stereotactic biopsies); these studies have argued that such surgical approaches have very little morbidity and may help guide therapy in patients with a presumed diagnosis of DIPG. In a recent change, tumor biopsies are now routinely performed at several European centers based on data from Roujeau et al, who reported very little morbidity associated with surgery in patients with presumed DIPG. Among 24 patients with imaging characteristics of an infiltrative diffuse pontine glioma, all underwent a suboccipital transcerebellar stereotactic biopsy. Two patients suffered deficits consisting of transient (< 2 months) new cranial nerve palsies and one of the patients also experienced an exacerbation of a preoperative hemiparesis. No patients died during the perioperative period. Twenty-two patients had a malignant infiltrative astrocytoma, one patient had a Juvenile Pilocytic Astrocytoma, JPA, and one patient had a low grade glioma. The diagnosis of the latter two affected the initial treatment after biopsy. Thus, this study demonstrated that stereotactic biopsy sampling is safe, with little morbidity and a high diagnostic yield. 13

In recent years, our understanding of the biology of these tumors has advanced considerably because of a concerted effort by North American oncologists to collect, and the willingness of families to donate, autopsy materials for study. The biological data obtained from autopsies can ultimately be compared to the European data obtained from biopsy specimens. Zargooni and Hawkins have shown that gains in platelet derived growth factor receptor (PDGFR) alpha occurred in 36% of patients with DIPG, and all showed PDGFR alpha expression. Low level gains in poly-ADP-ribose polymerase (PARP)-1 were identified in approximately 25% of cases. 14 Similar data has been reported by Paugh et al.15

3.0 RECRUITMENT, ENROLLMENT PROCEDURES AND ELIGIBILITY

3.1 Referral/Recruitment

3.1.1 Cincinnati Children’s Hospital Medical Center (CCHMC) will serve as the coordinating center for the Registry.

3.1.2 At CCHMC, patients and families will be recruited from the existing patient population.

3.1.3 Collaborating physicians and pathologists from outside institutions will be provided with information about the DIPG registry, information on how they can contribute data to the registry, and a DIPG registry brochure to give to families. For deceased patients, collaborating physicians will complete a release of decedent PHI form and send medical information to the Registry. Patients who wish to register on the International DIPG registry may call The International DIPG Registry office Monday through Friday 8:30am – 4:00pm EST, by calling (877-349-8074).

3.1.4 Registry personnel will schedule a time with the parent/guardian to obtain informed consent either over the telephone or in person.
3.1.5 Subjects and/or families may self-refer to the Registry. Registry personnel will obtain written consent/assent, as well as medical records release (HIPAA). Families of deceased patients may self-refer and may sign the DIPG HIPAA form for release of medical records and tissue samples (if available).

3.1.6 Deceased patients are eligible for inclusion in the Registry, per institutional policy. The Privacy Rule (45 CRF 164.512) allows the use or disclosure of protected health information for research on deceased individuals, provided that the researcher attests to the following: a) representation that the use or disclosure sought is solely for research on the protected health information of decedents; b) documentation at the request of the covered entity, of the death of such individuals; c) representation that the protected health information for which use or disclosure is necessary for the research purposes. A Request for Release of Decedent PHI form has been created for use with this registry. A ‘covered entity’ may request completion of their institutional form in place of the DIPG registry request form for release of Decedent PHI.

3.1.7 To allow non-English speaking patients to participate in this study, non-English consents or short forms will be IRB approved at CCHMC prior to use.

3.1.8 A Registry website will be developed and maintained to facilitate patient education, registry recruitment and enrollment, and to update the target audience on registry research and accomplishments. IRB approval of the web content regarding recruitment will be obtained prior to being publicly posted.

3.1.9 A recruitment brochure is available to inform physicians and families about the purpose and participation in the DIPG registry.

### 3.2 CONSENT/ASSENT PROCESS

3.2.1 It is expected that a telephone consent process will be used to obtain written consent for patients who are still living. An attempt will be made to obtain all consent signatures on the same date. If this is not feasible, the patient/guardian may mail the consent form back to CCHMC or fax it back when able. Upon receipt, the member of the study staff who obtained consent will sign the returned consent form.

3.2.2 For living patients referred from outside institutions, all consenting and data completion will be performed by delegated study staff at CCHMC. For International sites, local staff may obtain informed consent of living participants per institutional and country policies using site specific consent form approved by their ethics committee.

3.2.3 Medical records of referred patients will only be requested following consent to the Registry and obtaining the appropriate medical records release (HIPAA).

3.2.4 Written assent from living patients 11 years and older will be determined by the Institutional Review Board (CCHMC). Verbal assent will be obtained and documented in the informed consent process note. An exception to documented assent may occur in instances in which the child’s disease has led to physical or cognitive inability to provide assent, and such reasons for lack of assent should be clearly documented.

3.2.5 Participants and/or families will be given an opportunity to donate tumor tissue that is removed at the time of autopsy (if performed). A separate consent form or institutional autopsy consent form will be available for participants and/or families to sign for the storage and research use of the tumor tissue removed following an autopsy.

### 3.3 PATIENT ELIGIBILITY CRITERIA

3.3.1 All patients of any age (living or deceased) with a diagnosis (either current or past) of a
3.3.2 Unless the patient is deceased, all patients and/or one parent or legal guardian must provide written informed consent as well as HIPAA/release of information consent.

4.0 REGISTRY AND REPOSITORY PROCEDURES

Clinical data, imaging studies and pathology specimens may be submitted to the Registry/Repository by the treating/referring physician or local pathologist, or designee(s).

4.1 OUTSIDE INSTITUTION RESPONSIBILITIES FOR PATIENTS REFERRED TO THE REGISTRY/REPOSITORY

The process of obtaining informed consent and collection of registered patients’ medical information, radiographic imaging, and pathological material has been developed specifically to minimize work load burden at the referring institutions. CCHMC will be the main site to which referring physicians from outside institutions and self-referring patients will be directed. All regulatory and IRB approvals will be obtained and maintained at CCHMC. The Hospital for Sick Children in Toronto, Canada, and Sydney Children’s Hospital, Sydney Australia will serve as performance sites and will therefore maintain ethics board approval of the protocol. Outside physicians (not from Sick Kids, Sydney Children’s or CCHMC) who wish to take part in the registry and/or submit decedent PHI may notify their IRB of the site involvement per institutional policy.

CCHMC DIPG Registry coordinators will work with an identified designee from the referring center to obtain all pertinent source documentation including medical records, radiographic imaging on CD-ROM, pathological material (if available), and tissue for future research (if available). All data will be abstracted from the medical record by the CCHMC DIPG Registry team, who will be responsible for all CRF completion in the Registry database. Collaborating institutions may complete CRFs on site if their institution will not permit release of individually identifiable medical records of deceased and/or living individuals. A member of the DIPG Registry staff may also travel to a collaborating institution to collect medical information in accordance with the institutional policies.

Images submitted on CD-ROM will be de-identified, uploaded, and stored in the research PACS system housed at CCHMC. All paraffin blocks/slides submitted for central pathology review will be sent to CCHMC for digitization as described in section 4.5.

Frozen tissue submitted for future research will be sent directly to the DIPG Tissue Repository, which includes storage locations at CCHMC and at The Hospital for Sick Children, in Toronto, Canada. Frozen specimens originating from referring institutions in Canada will be sent to The Hospital for Sick Children and originating in Australia to Sydney Children’s Hospital for long-term storage. Frozen specimens originating from all other referring institutions will be stored at CCHMC.

4.2 Data Management and security

Once the DIPG registry coordinators receive all clinical material, a unique Registry number will be assigned to each case. The Registry database is password protected and only accessible by study staff. In addition, only one section of the Registry database will connect the Registry number with the personal identifiers. Access to this section of the Registry database is restricted to the DIPG Registry coordinator and other delegated Registry personnel.
4.2.1 DATABASE INFORMATION
The International DIPG Registry will utilize a Unified Registries Management (URM) module developed by Forte Research Systems (Madison, Wisconsin), a clinical trials management software system that has obtained caBIG™ Bronze Compatibility Certification from the NCI. CCHMC currently utilizes the Forte Research Systems’ Clinical Research Management solution which shares a platform with the URM module, making for seamless integration and operation. The underlying data structure can be oriented toward an event (e.g., biopsy/scan), condition (e.g., pain), diagnosis (e.g., DIPG), patient demographic (e.g., age/gender), or other concept. Additionally, relationships between records including familial, temporal, or taxonomic, may also be maintained. The integrity and quality of data collected is ensured through the use of standards. Electronic Data Collection forms are created using standard data elements. The URM data sharing model provides registry owners control over their own data while the exponential value of aggregated data encourages collaboration and data sharing. In addition, URM has the ability to create a de-identified version of a registry, one where the Protected Health Information (PHI) has been removed, also promoting data sharing by reducing restriction to data access based on privacy concerns. CRFs have been specifically developed to collect similar information that is currently being obtained in a mirror DIPG Registry in Europe.

4.2.2 CLINICAL DATA ELEMENTS
Data related to the following topics will be minimally collected from existing clinical records, pathology review, and imaging review:

Demographics
Diagnosis
Imaging at diagnosis
Physical exam at diagnosis
Treatment history
Response evaluations
Follow up data – ongoing response and relapse/progression/death
Central pathology review characteristics
Central imaging review characteristics
Molecular profile

4.3 RADIOGRAPHIC IMAGING CENTRAL REVIEW
All radiographic imaging submitted to the DIPG Registry will be de-identified, uploaded and stored in the research PACS system housed at CCHMC. Periodically, a panel of study neuroradiologists, will review all of the images submitted. Common data elements will be interpreted from the imaging and stored in the Registry electronic data system. The radiographic images will be stored indefinitely in the research PACS system with the patient’s assigned Registry number alone.

4.3.1 RESEARCH PACS INFORMATION
The radiology department has a dedicated research server for the storage of de-identified research images. It is 2 terabytes in size, and is expandable. At present it is accessible by password on the hospital network, viewed with the Amicas® PACS software. CCHMC may grant VPN access to the outside neuroradiologists to enable them to log onto the server and view the de-identified studies.

4.3.2 CENTRAL REVIEWERS
• Blaise Jones, MD, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
• James Leach, MD, Cincinnati Children’s Hospital, Medical Center, Cincinnati, OH
• Dawn Saunders, MBBS, Great Ormond Street Hospital for Children, London, United Kingdom
4.4 PATHOLOGY CENTRAL REVIEW

Deidentified pathology images (digitized slides) and pathology reports will be reviewed by a committee of Registry neuropathologists to confirm diagnosis of DIPG. Each member’s individual diagnosis determination will be included as data in the registry. Referring institutions will send all pathology specimens to CCHMC for digitization to enable this review.

The pathology specimens requested consist of glass slides (stained or unstained) and paraffin blocks of tumor tissue.

**Paraffin Blocks/ slides:** Submit representative paraffin embedded tissue blocks containing tumor. Please label blocks or slides with the institutional surgical pathology number and the patient’s DIPG study ID. If blocks are unavailable, send the following slides: Two (2) H&E stained slide of each block, Five (5) unstained slides of each block.

**Pathology Reports:** Institutional pathology report; photographs of representative gross lesions, if available, specimen transmittal form (with each shipment). DIPG registry staff may request results of any immunohistochemistry or molecular profiling that may have been performed for clinical purposes. DIPG staff will write the patient's DIPG study ID on the reports.

### 4.4.1 CENTRAL REVIEWERS

- Cynthia Hawkins, MD, The Hospital for Sick Children, Toronto, Canada
- Thomas Jacques, University of College London, Institute of Child Health, 30 Guilford Street, London
- Christine Fuller, MD, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH
- Pascale Varlet, Hospital Sainte Anne, Paris, France
- Pieter Wesseling, MD, PhD, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands

4.5 PATHOLOGY DIGITAL REPOSITORY

The Division of Pathology and Laboratory Medicine at CCHMC will be responsible for archiving digitized pathology cases. The management of digital slides will be adherent with HIPAA regulations, and the slides will be labeled with barcodes. The data is stored on a server, which is maintained and housed by the institutional IT service. This server is backed up by the IT service and currently has capacity for 4 terabytes of data, which is expandable. This system is designed to support multi-user, multi-site, or laboratory workflow-integrated deployments.

Each neuropathologist on the panel will have an account created, and receive instructions for using the software which runs inside their web browser. A specific user would only have access to the data group (s)he is authorized to access (i.e. DIPG pathology repository), all other data is protected.

### 4.5.1 TISSUE RETENTION AFTER DIGITIZATION

After the pathology slides are digitized, the specimens will be retained and stored in the DIPG tissue repository for future research. The tissue bank includes locations at CCHMC and at the Hospital for Sick Children in Toronto, Canada and Sydney Children’s Hospital in Sydney, Australia. Specimens originating from referring institutions in Canada will be sent to the Hospital for Sick Children after digitization at CCHMC. Specimens originating in countries outside of Canada will remain at CCHMC for long-term storage.

This tissue repository will serve as a resource for current and future research. In order for an investigator to receive any data or samples, a request form must be submitted to and approved as per the process outlined in section 6 and Appendix I. If the use of the samples and/or data released from the repository constitutes human subjects research per 45 CFR 46 or genetic
research, IRB approval will be required to be submitted with the investigator’s application. Proposals for decedent data or aggregate data will not require IRB approval.

4.6 SUBMISSION OF TISSUE FOR BANKING AND FUTURE STUDIES

In addition to storing pathology slides after digitization, the DIPG tissue repository will also receive and store fresh and/or frozen tissue for future research. Fresh and frozen tissue may be sent from referring institutions, when available, and will be stored in the DIPG tissue repository (as described in section 4.5.1). Sources of tissue may be from diagnostic biopsy, surgery or autopsy samples. Fresh tissue may be utilized immediately for biological studies that have been approved by the DIPG Scientific committee and appropriate IRB approvals/determinations have been received by the DIPG registry staff.

Specimens from referring Institutions in Canada will be sent to The Hospital for Sick Children in Toronto and tissue from Australia will be sent to Sydney Children’s Hospital. Tissue from referring institutions outside of Canada and Australia will be sent to CCHMC.

4.7 SUBMISSION OF BIOINFORMATICS DATA

Molecular data including, but not restricted to, genome-wide DNA copy number, karyotyping, expression profiling (mRNA and miRNA), methylation analysis, and DNA or RNA sequencing will be collated into an International DIPG Bioinformatics Repository (Cynthia Hawkins, MD). Molecular data will be obtained from any of the following sources:

- Data gathered retrospectively through a systematic review of published literature in DIPG, carried out according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.
- Collaborating investigators providing data to the DIPG registry will also be requested to provide any existing molecular data that has been collected for research and/or clinical purposes.
- Newly-generated data will also be incorporated by continual literature/database evaluation or direct submission of collaborating institutions.
- If molecular data have not been generated for tissue submitted to the DIPG Registry and if funds are available, molecular analyses, including but not limited those listed above may be performed on this tissue. Data generated will be deposited directly into the DIPG Bioinformatics Repository.

Researchers with publications identified by this systematic review will be invited to contribute any relevant data in addition to that which may be found in the published literature or databases. Investigators known to have unpublished data will be approached to contribute pre-publication. Data may be held in this context in a non-public (password-controlled) area.

Sample identifiers will be linked to those that appear in the Registry to allow for the correlation of molecular and clinico-pathological variables. The DIPG registry staff at CCHMC will maintain the link between the site ID and the assigned DIPG registry number. The repository will be held at the genomic data facility at the Hospital for Sick Children, Toronto Canada under the direction of Cynthia Hawkins, MD. Both original raw data and processed files will be requested, and can be uploaded along with annotation files to a secure ftp site.

By combining these data, we intend to generate a comprehensive, accessible database of the molecular profiles of DIPG for the academic community. Initial collaborative analyses will be undertaken as part of this project, with the following goals:

- create a low-resolution fully integrated dataset to define the frequencies of chromosomal alterations
- retain the original platform-specific data to accurately map amplification/deletion breakpoints
- compare the data with publicly available pediatric and adult high-grade glioma datasets
• investigate any retrospective clinicopathological correlations of the genetic aberrations identified
• better define the intrinsic subgroups of the disease based upon genomic, epigenomic, and transcriptomic signatures
• integrate expression and genetic/epigenetic data with the copy number studies

Data generated from biospecimens contributed to the Registry, will also be incorporated into the repository in a prospective manner, with due consideration given to the most appropriate platforms for data generation and integration with the repository.

5.0 STATISTICAL ANALYSIS

There are no statistical considerations or sample size goal for this protocol. The anticipated annual accrual is 150 patients per year. Statistical justification will be required of all research requests made to the International DIPG Registry for release of data, imaging, or specimens for research projects. The protocol will remain open indefinitely.

6.0 PROCEDURE FOR APPLICATION TO THE REGISTRY FOR DATA OR SPECIMEN RELEASE

Clinical, radiographic, pathologic data and biological specimens may be released to qualified investigators after a subset of the study committee for this protocol has judged their proposals for scientific merit, clinical priority, and feasibility as outlined in the DIPG Registry Constitution. The Study Chair will select a group (up to three reviewers) with appropriate scientific and regulatory/ethics knowledge that are most distant from conflict with the proposal. The study coordinator will maintain documentation of the review and approval/refusal.

The use of these cooperatively acquired data elements and tissue specimens constitutes collaboration, and researchers and the International DIPG Registry Committee must agree upon a “Collaborative Research Agreement” prior to release of specimens. This agreement will outline at a minimum the data and/or specimens to be provided, the agreed upon uses of the data/specimens, and what is to be done with the data/specimens once the research has been completed. Note that patient-identifying data/specimens will never be released to investigators.

7.0 INTERNATIONAL DIPG REGISTRY AND REPOSITORY SCIENTIFIC REVIEW COMMITTEE MEMBERS

Refer to the DIPG Registry Constitution for a full list of scientific review committee members, review processes and procedures. Members of the DIPG registry executive and scientific committee but may change in accordance with the DIPG registry constitution.

8.0 RISKS AND BENEFITS OF THE STUDY

The study does not offer personal benefit to subjects. The study will benefit future DIPG patients by fostering collaboration and data sharing among investigators. This will improve future research studies and classification systems, standards of diagnosis, assessment and response, ultimately leading to the development of more effective therapies for children with DIPG.

This study poses minimal risk to subjects. Risks include the possible loss of privacy regarding personal
health information. This risk will be minimized as described in section 4 of this protocol. There are no medical interventions or physical risks associated with this study.

8.1 RISK/BENEFIT ANALYSIS

This study poses minimal risk and offers no direct benefit to participants.

8.2 CHILDREN AS REGISTRY PARTICIPANTS

The vast majority of DIPG patients are children, therefore, it would not be possible to create a DIPG registry without child participation. When feasible, assent will be obtained, as noted in section 3.2.3. Because the study risk is minimal, and because this registry offers advantages to the DIPG population as a whole, assent will not be required when it is not feasible based on cognitive/physical disability or age. Parent permission will be required for participation and assent will be obtained whenever possible. Risk will be minimized as described in section 4.2 of this protocol.
APPENDIX I. INVESTIGATOR APPLICATION INSTRUCTIONS

Investigators who wish to obtain data from the International DIPG Registry should supply all information as outlined and enclose the indicated appendices. The outline should be followed completely. The information requested is necessary to ensure that your request is properly reviewed for scientific merit, clinical relevance, feasibility, and priority.

PLEASE INCLUDE:

1. Project Title:

2. Investigator(s):
   Investigator(s) contact information including:
   Institution, Address, Phone, Fax, Email.
   Hours available and time zone.
   Shipping address if different than above.

3. SPECIFIC AIMS - Briefly indicate the scientific questions to be answered by the proposed research.

4. BACKGROUND AND RATIONALE - Provide background information and the scientific rationale for the problem you hope to study. Include a relevant bibliography. Background information should be sufficient to clarify the rationale for the study -- about two or three paragraphs in length.

5. PREVIOUS EXPERIENCE – Previous experience and results that relate to the proposed research.

6. RESEARCH DESIGN - 1) Organize this section according to the Specific Aims. 2) What data will be required (exact nature and number). 3) How the study will be performed. If the data analysis methods are well recognized and thoroughly described in the literature, cite references. Otherwise, please describe these in detail. All proposals are required to provide justification for the number of data elements requested.

7. FUNDING INFORMATION - Requests for data may be prioritized. If so, data will be provided to investigators on a rotating basis in the following priority order: Peer reviewed funded investigators (including Federal and National Laboratories), New Investigators and academic investigators developing new research projects, and other investigators.

8. Please supply a copy of each of the following:
   A. NIH Biographical Sketch or current CV (updated within past 2 years)
   B. Signed Research collaborative agreement and other agreements as applicable (ie., Material Transfer agreement or Data Use Agreement).
   C. Institutional Review Board approval or a letter from the chairperson of the IRB must accompany this application if research request constitutes human subjects research per 45 CFR 46 or research request involves genetic research.
      Research proposals for data from deceased individuals will not require IRB oversight. Proposals for which only aggregate data is requested or complete statistical analysis occurs at CCHMC will not require IRB oversight as no individual data points will be released from the registry.
REFERENCES


