International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Types I, II and III PPB

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ABSTRACT

Background: Pleuropulmonary blastoma (PPB) is a rare malignant neoplasm of the lung presenting in early childhood. Three pathologic “Types” are recognized. The Types are manifestations of one disease along a time spectrum from birth to age ~72 months (7% of cases occur after age 72 months). Type I PPB is an air-filled purely cystic neoplasm (median diagnosis age 10 months) for which treatment is surgery with or without adjuvant chemotherapy. Type II PPB (cystic/solid) and Type III PPB (solid) are aggressive sarcomas (median diagnosis ages 33 and 44 months, respectively) for which treatments are surgery and multi-agent chemotherapy with or without radiation therapy.

PPB has strong genetic implications with a unique set of associated neoplasia and dysplasia in the patient or family occurring mostly in childhood and adolescence. Lung cysts and cystic nephroma are the most common associated conditions. The International PPB Registry (IPPBR) has recently reported germline loss-of-function mutations in the gene *DICER1* in PPB patients and family members.¹,²

There has never been a large prospective study of PPB therapy. It is estimated that 30-50 cases of Type I PPB and 40-60 cases of Types II and III PPB are diagnosed annually worldwide. Consultations among international pediatric sarcoma experts concluded that because of (1) the rarity of PPB, (2) regulatory complexity and (3) regulatory differences between countries, a prospective treatment study could not be organized.

Therefore, to collect a large group of Types I, II and III PPB patients for event-free and overall survival analysis, this project is organized as a “Treatment and Biology Registry” for the collection of treatment data on patients for whom therapy decisions are made by each institution.

PPB therapy choices are the decision of each institution. This Treatment and Biology Registry presents surgery and chemotherapy guidelines. Through this Registry, it is anticipated that analysis of a group of similarly treated children with PPB will advance the knowledge of effective ways to treat PPB.

Treatment and Biology Registry Design and Goals:

- **Type I PPB**: Type I PPB is an early manifestation of this malignant disease, cured in some cases by surgery. Therapy decisions are the responsibility of the treating institution. Surgical guidelines are presented. It is unknown whether adjuvant chemotherapy improves cure rates for Type I PPB patients. If the treating physicians select adjuvant chemotherapy treatment, the Treatment and Biology Registry guideline is a 41-week “VAC” regimen.

- **Types II and III PPB**: Types II and III PPB are aggressive sarcomas. Surgery and chemotherapy are necessary in all cases. Specific therapy decisions are the responsibility of the treating institution. Surgical guidelines are presented. The Treatment and Biology Registry chemotherapy guideline is a single-arm multi-agent chemotherapy neo-adjuvant/adjuvant regimen (“IVADo”) for 36 weeks. Second and
possible 3\textsuperscript{rd} look surgery may be considered for local control. Radiation therapy for unresectable focal residual disease is an option for local institutional decision.

- **PPB-Associated Diseases:** An unusual feature of PPB is that in a large number of cases, the PPB patient or other young family members have other tumors or malformations. Because PPB and the associated conditions found in PPB families suggest a familial tendency to formation of tumors, it is scientifically important to collect information on the associated conditions. The International PPB Registry can use its procedures to collect information on these cases.

- Diagnostic pathology consultation is strongly encouraged, but enrollment in this Registry relies on local diagnosis. Retrospective central pathology review is required.

- The Treatment and Biology Registry will generate overall and event-free survival data (a) for Type II and Type III PPB patients, where pathology is confirmed by central review and treatment is uniform and (b) for Type I PPB patients where pathology is confirmed by central review, comparing those who received or did not receive chemotherapy. Results will be compared to historical controls to provide the basis for future studies for this disease.

- Collection of biologic specimens including fresh, frozen or preserved tumor is encouraged for further research into the biology of PPB.

Parental consent for data and specimen collection by the Registry is required for all enrollees (also HIPAA in the USA).

### 1.0 SPECIFIC AIMS

1.1 To enroll and follow Type I PPB patients for event-free and overall survival (EFS, OS), progression, and recurrence. Use of chemotherapy will be decided by the treating physician/institution.

1.2 To enroll and follow Types II and III PPB patients for EFS and OS, progression and recurrence. Maximum attempts at surgical resection are suggested. A single-arm neoadjuvant/adjuvant chemotherapy regimen is the chemotherapy guideline in this Registry. Radiation therapy for unresectable focal residual is optional and decided upon by the treating institution.

1.3 To provide surgical guidelines for Types I, II and III PPB.
To enroll and follow patients with conditions associated with PPB, but who do not have PPB.

1.5
To establish a PPB Biologic Specimens Collection for research uses: collect family medical history and fresh, frozen and preserved PPB tumor. (See §2.5.2).
2.0 BACKGROUND AND RATIONALE

2.1 General Considerations

PPB Overview: PPB is a rare and unique childhood malignancy, first described in 1988. PPB is a dysembryonic malignancy believed to arise from pleuropulmonary mesenchyme. It is recognized as the pulmonary analog of more common childhood developmental neoplasms such as Wilms tumor of kidney (nephroblastoma), hepatoblastoma, neuroblastoma, embryonal rhabdomyosarcoma and medulloblastoma. Like these, most cases of PPB (93%) are diagnosed in children less than 6 years of age.

The International Pleuropulmonary Blastoma Registry: The International Pleuropulmonary Blastoma Registry (IPPBR) (www.ppbregistry.org) was formed in ~1987. The IPPBR is a collaboration between the Pediatric Oncology Department of Children’s Hospitals and Clinics of Minnesota, Minneapolis, MN, USA; the Department of Pathology, Children’s National Medical Center, Washington, D. C., USA, and the departments of Surgical Pathology and Cancer Genetics at Washington University Medical Center, St. Louis, MO, USA. These institutions have also collaborated on genetic and molecular studies of PPB. Approximately 400-500 cases of PPB have been recorded since the initial description, comprised of 260 pathology-confirmed IPPBR cases (March 2009) and approximately 200-250 other cases in the medical literature. Children with PPB have been treated diversely according to local therapy decisions. There has never been a large prospective study of PPB treatment or a large collection of PPB patients treated consistently.

2.2 Pleuropulmonary Blastoma (PPB)

2.2.1 PPB Pathologic “Type” Definitions

PPB is divided into three pathologic subtypes representing a progression of the disease along an age-related biologic continuum from birth to age ~72 months (93% of cases).

Type I PPB is an air-filled entirely cystic neoplasm occurring generally in peripheral lung parenchyma or visceral pleura. Type I PPB is a subtle malignancy with typically only scattered malignant cells beneath a benign epithelial cyst lining. (see Pathology description §2.2.4)

Type Ir PPB is a newly-recognized cystic manifestation of PPB. It is not considered malignant. It is rare and found usually, but not exclusively, in relatives of PPB patients. Type Ir cysts may also rarely be found in a PPB patient’s lung separate from the frank manifestations of Types I, II, or III PPB. The “Ir” designation represents Type I “regressed”. (Type Ir diagnosis is highly specialized; consultation with IPPBR pathologists is suggested.)

Type I PPB with features of regression is newly recognized by International PPB Registry pathologists. It is a judgment by experienced PPB pathologists that the particular Type I case may, over time, become a Type Ir PPB. Because there is uncertainty whether chemotherapy...
should be used for any Type I PPB, the International PPB Registry has been specifically suggesting to clinicians that chemotherapy not be used for cases interpreted as “Type I PPB with features of regression”. Real-time referral of Type I PPB cases is strongly encouraged to evaluate this possibility.

Type II PPB is a cystic and solid neoplasm. Cystic portions are identical to Type I PPB. The solid elements are an aggressive mixed-pattern sarcoma. It also occurs generally in peripheral lung parenchyma or visceral pleura. (see Pathology description §2.2.4).

Type III PPB is an entirely solid aggressive mixed-pattern sarcoma. It occurs in lung parenchyma, visceral pleura and parietal pleura. (see Pathology description §2.2.4).

2.2.2 PPB Biology and Genetics
PPB biology is unique among pediatric malignancies with its age-related cystic, cystic/solid and solid expressions. There is strong evidence that Types I, II and III PPB are related on a time spectrum from the neonate to approximately age 72 months (93% of cases), although diagnosis of each Type and progression may rarely be discovered up to approximately age 20 years. Evidence for the PPB Type continuum is as follows5: PPB Type is correlated with age; PPB not eradicated at one stage can evolve into more advanced disease; histologic complexity and malignancy increases as Type progresses; tendency to metastasis increases with Type,5 prognosis worsens as Type progresses.

PPB is a strongly genetic disease. A wide and unusual set of dysplasia and neoplasms, known as the PPB Family Tumor Susceptibility Syndrome,6-9 are found in the PPB patient or the family in ~40% of IPPBR cases. Several families with multiple PPB cases are known. Particularly common in these children and kindreds are multifocal and/or bilateral lung cysts and cystic nephroma (found in 9-10% of IPPBR cases of PPB).7 The complete phenotype for this syndrome is not yet described. The IPPBR and colleagues at Washington University St. Louis reported in April 2009 germline, loss-of-function mutations in the gene DICER1 in 11 of 11 PPB families studied.1,2 The IPPBR continues actively to explore the implications of this finding (http://www.ppbgeneticstudy.org).

2.2.3 PPB Clinical Manifestations
Type I PPB: In the IPPBR experience, Type I PPB occurs from birth though age 114 months, but typically in the first 3 years of life; the median diagnosis age is 10 months. Patients may present with the cyst as an incidental finding on radiograph or with respiratory distress from a large cyst or pneumothorax. Type I PPB cannot be distinguished radiographically from benign congenital lung cysts, although pneumothorax and the presence of multifocal or bilateral cysts suggests PPB.6 Also, the presence in the patient or family of any disease associated with PPB (section 2.3) strongly suggests a cyst is PPB.6

Types II and III PPB: Type II PPB may present like Type I PPB as an incidental finding or with respiratory distress from cyst or pneumothorax. More commonly, Types II and III PPB present as “pneumonia” with an ill child: fever, lethargy, cough, an opaque finding on chest radiograph. The child does not improve on antibiotics and further investigation (usually chest
CT scan) reveals a mass. Type II and especially Type III PPB are typically extensive tumors, often involving an entire hemithorax.

**Metastasis in PPB:** Metastasis of Type I PPB has not been reported. Types II and III metastasize most frequently to brain parenchyma; life-table projected 5-yr incidence estimates for cerebral parenchymal metastasis for Type II PPB is 11% and for Type III PPB is 55%. Cerebral spinal fluid disease is very rare, but has occurred in 3 recent IPPBR cases. In fewer than 5% of cases, PPB metastasizes to bone, liver, and lung parenchyma. Metastasis documented at the time of diagnosis is rare but occurs. Bone marrow disease is very rare; one case documented among 133 IPPBR–reviewed Types II and III cases. Most metastases occur within 24-36 months of diagnosis; metastasis more than 36 after diagnosis is unusual.

### 2.2.4 PPB Pathologic Diagnosis

**Type I PPB**

Type I PPB, occurring in the youngest children, is an entirely cystic tumor. Pre-operatively, malignancy is rarely suspected. The cyst is usually a multilocular cyst in peripheral lung.

Microscopically, the cystic structure of Type I PPB may appear unicystic in the gross examination but has a characteristic multilocular architecture with delicate septa at low magnification. A diagnostic population of small primitive mesenchymal cells is found in the stroma beneath the benign epithelial lining; these cells may be a localized single focus, several foci or a diffuse proliferation resembling the cambium layer effect of a sarcoma botryoides. The primitive small cells may display rhabdomyomatous differentiation as seen in an embryonal rhabdomyosarcoma. When there is rhabdomyoblastic differentiation, cells with prominent eosinophilic cytoplasm may be present. Small nodules of immature cartilage may be found in the septa and are not necessarily accompanied by the small primitive cells. Because the small primitive cells or nodules of cartilage are present only focally in some cases, it may be necessary to submit an entire cyst specimen for microscopic examination. Anaplastic cells are rarely found in Type I PPB.

**Type Ir PPB** is a newly-recognized cystic manifestation of PPB. It is not considered malignant. It is rare and found usually, but not exclusively, in relatives of PPB patients. Type Ir cysts may also rarely be found in a PPB patient’s lung separate from the frank manifestations of Types I, II, or III PPB. The “Ir” designation represents Type I “regressed”. (Type Ir diagnosis is highly specialized; consultation with IPPBR pathologists is suggested.)

**Type I PPB with features of regression** is newly recognized by International PPB Registry pathologists. It is a judgment by experienced PPB pathologists that the particular Type I case may, over time, become a Type Ir PPB. This has implications for the clinicians’ decision whether to use chemotherapy for Type I cases. Real-time referral of Type I PPB cases is strongly encouraged to evaluate this possibility.

**Types II and III PPB:** The cystic portions of Type II PPB are similar to Type I PPB. The histologic findings in the solid portions of Types II and III PPB are typically those of a mixed pattern aggressive sarcoma including embryonal rhabdomyosarcoma, chondrosarcoma, fibrosarcoma-like areas, undifferentiated blastema, anaplasia, and occasional other sarcoma.
subtypes. Necrosis is common. Apparent “cysts” resulting from necrosis are “pseudocysts” and are not diagnostic of the epithelial lined cysts required for a designation of Type II cystic/solid disease. Anaplasia, similar to anaplasia in Wilms tumor, occurs in 75% of Type II and 85% of Type III PPB. Lymph node involvement is very rare. The cytology of pleural effusions is rarely diagnostic.

Trisomy 8 is common in PPB but not specific. The IPPBR and colleagues at Washington University St. Louis reported in April 2009 germline, loss-of-function mutations in the gene DICER1 in 11 of 11 PPB families studied.

2.2.5 PPB Historical Treatments and Prognosis
There have been no large prospective studies of PPB treatment nor any large collections of PPB patients treated consistently. Series reporting more than 10 patients have been retrospective collections of patients treated heterogeneously. Nine Type II and III PPB patients were treated prospectively in Italian Rare Pediatric Tumor studies (AIEOP-TREP), as discussed below.

2.2.5.1 Type I PPB: Historical Treatments and Prognosis
Historically, Type I PPB treatment has consisted of surgery with or without adjuvant chemotherapy. Treatments have been decided locally and have been heterogeneous. There are no prospective studies.

A retrospective, multi-institution collection of 38 Type I PPB cases suggests a benefit to adjuvant chemotherapy. Among the 38 cases, 18 were treated with surgery plus adjuvant chemotherapy; of these 18, one PPB recurred and the child died. Twenty patients had surgery alone; 8 (40%) recurred and 5 of those died. All recurrences were Type II or III PPB. Event-free survival was higher in the surgery + chemotherapy group (p = 0.01); overall survival did not differ significantly (p = 0.18). Kaplan-Meier overall survival for 38 children was stable at 85-90%. Most of these patients included in this collection were treated (1) before PPB was a well-known neoplastic entity and (2) before the natural history of PPB was well recognized, particularly the tendency of Type I disease to progress to Types II or III disease. Therefore, most patients did not have a “cancer operation” and were not followed closely for recurrence.

An alternative to managing Type I PPB with surgery plus adjuvant chemotherapy is to perform complete resection and encourage frequent surveillance for early recurrence. Perhaps early-diagnosed recurrence or progression of Type I PPB can be successfully treated with additional surgery and chemotherapy. There is no data for estimating the success of such a “salvage” approach to recurrent/progressive Type I PPB.

2.2.5.2 Types II and III PPB: Historical Treatments and Prognosis
Historically, Types II and III PPB have been treated as sarcomas similar to rhabdomyosarcoma. For many years, attempted surgical extirpation was followed by various adjuvant therapies. More recently, because many PPBs are very large and because neo-adjuvant chemotherapy can reduce the volume of other tumors, PPB has been approached with biopsy, neo-adjuvant chemotherapy, extirpative surgery and further adjuvant therapies. In “biopsy-first” cases, chemotherapy may result in >90% volume reduction. Responses are
seen after the first 2-4 courses of neo-adjuvant therapy and can be lost; anaplastic cells are the least responsive to chemotherapy. Surgery should be performed after 2-4 courses of neo-adjuvant therapy (unpublished IPPBR observations). No data is available to compare cure or metastasis outcomes for initial biopsy versus initial resection strategies.

In the United States, chemotherapy treatments for PPB have typically involved vincristine (V), dactinomycin (A), cyclophosphamide (C), often with the addition of doxorubicin (Adriamycin®) (Ad) and/or cisplatin (Plat). Typical regimens have been VA, VAC, VACA (= VACAd = VAC alternating with VAdC), or VAC/PlatAd (VAC alternating with PlatAd). In Europe, the tendency has been to use ifosfamide (I) more than C, epirubicin (Ep) or Ad, carboplatinum (Carbo) instead of Plat, and in some regimens to add etoposide (Et). Typical regimens in Europe have been denoted VA, VAI, “VAIA” (= VAIAd = VAI alternating with VAdI), “EVAIA” (= EtVAIAd, and “CEVAIE” (= CarboEpVAIEt = alternating VAI, CarboEpV and VIEt). “ICE” (= ICarboEt) has also been used. Radiation therapy has been typically reserved for residual foci of disease not amenable to resection.

In a 1997 report of 50 cases, treated from approximately 1975 to 1995 using the typical agents listed above used in the United States, overall 2-yr survival for Types II and III PPB was 73% and 48%, respectively. The 5-yr overall survival for Types II and III was approximately 45% and 35%, respectively. These differences did not reach statistical significance. No specific chemotherapy agent or regimen could be shown to be especially effective.

The Italian Rare Tumor Group (AIEOP-TREP) has published 22 PPB cases accessioned from 1982 to 2005, including 3 Type I, 6 Type II, 12 Type III cases (one Type unknown). Type II and III patients were treated with VAIAd or CarboEpVAIEt with radiation in three cases, including 9 patients entered prospectively after 1998 who received VAIAd (VAI alternating with VAdI). Overall Kaplan-Meier 5-yr survival, including the three Type I cases, was 49%.

The German Soft Tissue Sarcoma Group has described in abstract form 19 Type II and III PPB cases accessioned from 1981 to 2007. Treatments were VACAd, VIA, VAIAd, EtVAIAd, or CarboEpVAIEt with radiation in 5 cases. Overall Kaplan-Meier 5-yr survival was 70%. It is not clear why this series has notably better survival than the two series noted above. The German Soft Tissue Sarcoma Group advocates extirpative surgery, “VAIA” (“VAIAd”) chemotherapy and consideration of focal radiotherapy for unresectable residual for Types II and III PPB (Kirsch/Koscielniak personal communication).

In an unpublished 2006 analysis by the IPPBR, the chemotherapy of 137 Types II and III PPB patients was evaluated. This case population was comprised of 102 pathology-reviewed IPPBR cases, 16 cases reported by Kirsch, which were not differentiated as to Type II vs. III, and 19 cases reported by Indolfi. There were 64 Type II cases, 52 Type III cases and 21 Type II/III NOS cases. This analysis suggests that vincristine, dactinomycin, ifosfamide and doxorubicin are more active in PPB than other agents.

For Type II PPB, the historical Kaplan-Meier estimates of EFS and OS at 60 months are 50 and 58%, respectively. For Type III PPB, EFS and OS at 60 months estimates are 32 and
50%, respectively [unpublished IPPBR data].

2.2.6 PPB Therapy Plans in the Treatment and Biology Registry

2.2.6.1 Type I Cystic PPB in the Treatment and Biology Registry

2.2.6.1.1 Enrollment: Type I PPB patients will be enrolled in this study and followed prospectively.

2.2.6.1.2 Surgical Guidelines: (see § 4.1.1). Complete surgical excision of Type I cystic lesions is recommended if at all possible, but it is recognized that some children have such extensive multifocal and/or bilateral cystic change that complete removal of cysts is not possible.

2.2.6.1.3 Chemotherapy Guidelines-Type I PPB: The decision whether to use chemotherapy for Type I PPB will be made at the local institution. Because of the tendency for PPB to progress over time, the pathology of “late” Type I PPB merges with “early” Type II PPB. Therefore, before a final decision on use of chemotherapy, real-time pathology consultation with IPPBR pathologists for Type I cases is encouraged. (see Background sections on Pathology (see §2.5).

If an institution elects to use chemotherapy for Type I PPB, the Treatment and Biology Registry guideline for Type I PPB is “VAC” chemotherapy for 41 weeks. This recommendation is based on recent low- and moderate-risk rhabdomyosarcoma regimens and experiences. Neo-adjuvant low-risk regimens limiting cyclophosphamide have been complicated by early on-therapy recurrence; although there is no directly comparable experience with Type I PPB, recurrences of Type I PPB have been advanced Type II and III PPB. If chemotherapy is used for Type I PPB, the International PPB Registry opinion is that it should be more intense than a regimen which has allowed on-therapy recurrence in low-risk rhabdomyosarcoma.

Surveillance Recommendations for Type I PPB are offered in this Treatment and Biology Registry based on time to recurrence/progression data.

2.2.6.2 Types II and III PPB in the Treatment and Biology Registry

In preparation for an international effort to analyze the treatment of PPB, a meeting was convened in Geneva, Switzerland in September 2006. Representative from France, Germany, Italy, United Kingdom, and the United States were present. Since then additional communications followed which resulted in this Treatment and Biology Registry.

Because the number of PPB patients worldwide is small and because there is insufficient data for stratification by prognostic group, representatives agreed that PPB Types II as III should be treated with a single-arm chemotherapy regimen. Regimens and duration of therapy were considered. V, I, A, and Ad were agreed upon as the most important agents for PPB. VAIAd
and IVADo were considered. VAIAd and IVADo involve the same agents; however, VAIAd is alternating cycles of VIA and VIAd, whereas IVADo employs all four drugs in the first four cycles of therapy; IVA is used thereafter. A minority of conference participants believed VAIAd should be recommended. The IVADo regimen for 36 weeks was chosen because of the four chemotherapy agents involved and because the up-front dose intensity of IVADo may be especially useful in neo-adjuvant setting.

Since February 2007, when contacted by physicians treating PPB, the IPPBR has recommended IVADo therapy for Types II and III PPB patients. Twenty-four patients have been treated through November 2008. The results are preliminary but responses and outcome so far suggest that IVADo is at least as useful as one could expect compared to heterogeneously-treated historical controls.

2.2.6.2.1 Enrollment: Types II and III PPB patients will be enrolled in this Treatment and Biology Registry and followed. Cases of Types II and III PPB, which are recurrences of Type I PPB not previously treated with chemotherapy, will also be enrolled and followed.

2.2.6.2.2 Surgical Guidelines: Surgical (and biopsy) Guidelines are presented. Local disease control with 2nd and if necessary 3rd look surgical procedures is suggested by this Treatment and Biology Registry. (§ 4.1.1)

2.2.6.2.3 Chemotherapy Guidelines - Types II and III PPB: Institutions, perhaps in conjunction with coordinating pediatric oncology associations, will decide locally what therapy to use for Types II and III PPB. Because of the rarity of PPB and insufficient data on prognostic factors for Types II and III disease, the Treatment and Biology Registry does not recommend stratification of treatment. The Treatment and Biology Registry chemotherapy guideline is a single-arm chemotherapy regimen: “IVADo” for 36-weeks (neo-adjuvant/adjuvant chemotherapy when biopsy is chosen for initial diagnosis).

2.2.6.2.4 Radiation Therapy: Whether to use radiation therapy for focal unresectable residual disease will be decided by local institutions.

Therapy for recurrence after Types II and III PPB is not included in this study, but patients will be followed for outcome and institutional choices will be collected.

2.3 PPB-Associated Diseases in PPB Patients and Families and Genetic Factors in PPB Patients and Families

Early childhood onset of PPB, multifocal and bilateral pulmonary cysts/tumors, and an increased incidence of rare, primarily pediatric tumors in PPB patients and close family members suggest a strong genetic component in PPB biology. Current IPPBR data suggest that ~40% of children with PPB have a predisposition to neoplasia and/or dysplasia, known
as the PPB Family Tumor Susceptibility Syndrome. Particularly common in these children and kindreds are multifocal and/or bilateral lung cysts and cystic nephroma (found in ~10% of IPPBR cases of PPB). The IPPBR and colleagues at Washington University St. Louis reported in April 2009 germline, loss-of-function mutations in the gene DICER1 in 11 of 11 PPB families studied. The IPPBR and collaborators continue to explore the extent and implications of this mutation in the PPB Family Tumor Susceptibility Syndrome (http://www.ppbgeneticstudy.org). This syndrome is not similar to the other known childhood tumor predisposition syndromes such as the Li-Fraumeni, Beckwith-Wiedeman, and Wilms-aniridia.

This study includes collection of family medical histories and biologic specimens on patients and parents (see § 2.5) for research into the biology of PPB.

Because PPB and the associated conditions found in PPB families suggest a familial tendency to formation of tumors, the IPPBR will collect information on the diagnosis and treatment of these conditions on the “associated conditions” arm of this study.

2.4 PPB Type versus IRS Clinical Group versus TNM staging

In evaluating patients for outcome, the IPPBR and most other investigators have evaluated PPB cases according to PPB Types I vs. II vs. III. The IPPBR has not used the Intergroup Rhabdomyosarcoma Study (IRS) “clinical group” classifications (Ia and b, IIa and b, IIIa and b, and IV), which are assigned after complete radiological staging, initial surgery and pathological examination.

Establishing an “IRS-type” clinical grouping system for PPB is a challenge because PPB is very different from most rhabdomyosarcomas originating in specific muscle sites. Difficulties are as follows:

- Precise anatomic localization of PPB primary site is often difficult or impossible: lung, visceral pleura, parietal pleura.
- How does one integrate Types I, II, and III PPB into “groups”?
- PPB often involves an entire hemithorax and CT does not yield details of radiographic staging in the way that MRI can define extent of involvement of muscle planes for typical rhabdomyosarcomas.
- How are multifocal cysts and/or bilateral cysts, which are a unique part of PPB biology, factored into the grouping?
- How does one classify tumor spill? Pleural Effusion? Involvement of a contiguous lobe? Involvement of parietal pleura?
- Nodes are almost never involved with PPB and are difficult to image intrathoracically.
- Will detailed grouping of some PPB cases be useful if many cases are only biopsied?

Notwithstanding these difficulties, it is reasonable for a prospective study of PPB treatment to attempt consistent staging procedures and to compare PPB-adapted IRS-type clinical
grouping to PPB Types for prognostic importance. The IPPBR is attempting to classify cases retrospectively using a PPB-adapted clinical group-TNM staging system. The system being used is presented in Appendix I.

2.5 Central Pathology Review and Biology Studies

2.5.1 Central Pathology Review
Treatment and Biology Registry enrollment will be based on local diagnosis, but central pathology review is required. Central review is critical for correct identification and classification of PPB, for the standardization of future protocols that base treatment strategies on PPB Type classification, and for research studies which may correlate novel prognostic markers with clinical and pathologic data. Central review of post-chemotherapy resection tissue and metastatic tissue is strongly encouraged. (For submission details, see Appendix A-II: 1.1). Central pathology review is also critical for cataloging diseases identified as being associated with PPB.

2.5.2 PPB Biology Studies
Primary goals of this biology research are (1) to identify new clinical, pathological and molecular factors that predict outcome in order to create risk-appropriate treatments in the future and (2) to establish a collection of PPB biologic specimens for future research.

The objectives of the biology studies are:

(1) to classify patients by age, pathologic Type, histopathologic features, tumor invasiveness, presence of metastasis.

(2) to collect information on family medical illnesses, in order to refine the clinical characteristics of the PPB Family Tumor Susceptibility Syndrome.

(3) to establish a collection of PPB, and conditions associated with PPB, biology specimens (tumor tissue) for future research into the biology of PPB.
3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Treatment and Biology Registry Review and Approval by Human Subjects Committee (Institutional Review Boards, Helsinki Committees)

Because PPB is rare, many institutions will not prospectively review a study of PPB therapy. In addition, differences between countries make formation of an international treatment trial very difficult. Therefore a traditional, multi-institution prospective treatment trial is not feasible.

Formulating this project as a Treatment and Biology Registry provides flexibility in collecting cases from institutions with differing regulatory environments or review-board practices. Parental consent is required. In the United States, HIPAA consent is also required. Many institutions will allow direct parental consent to and enrollment in this Treatment and Biology Registry. Some institutions will require Human Subjects Committee, Institutional Review Board or Helsinki Committee approval in addition to parental consent. Therefore, several scenarios leading to case participation in the Treatment and Biology Registry are possible – see Appendix III.

Treatment and Biology Registry consent forms, including an “Assent” form (for older children), and HIPAA consent are in Appendix IV.

3.2 Patient Enrollment

To enroll a patient, contact the Treatment and Biology Registry office at the IPPBR office via email gretchen.williams@childrensmn.org or by fax. The enrollment form found in Appendix VII. A unique study patient identifier number will be assigned after the registration process.

Also, parents may enroll their child by sending to the Registry office (fax or pdf or mail) a signed Consent Form (Appendix IV). The Registry will then contact the treating institution for further information.

3.3 Eligibility Criteria

3.3.1 Age
Patients from birth to \( \leq 21 \) years of age at the time of diagnosis will be included in the Treatment and Biology Registry.
Patients of any age will be included in the Associated Diseases arm of this study.

3.3.2 Pathology Diagnosis
Patients with newly-diagnosed PPB Types I, II or III. Diagnosis is made by the local
pathologist. Real-time central pathology review is encouraged but is not required. All cases must be submitted for central pathology review. Only centrally-reviewed cases confirmed as PPB will be analyzed prospectively.

Cases in which the initial diagnosis is “suggestive” or “supportive” of PPB, but not diagnostic, and in which later resection specimens, including resections following chemotherapy, confirm a PPB diagnosis will be included. Patients diagnosed by fine needle aspiration biopsy will be included only if a later resection specimen, including resections following chemotherapy, is diagnostic of PPB.

Diagnostic pathology for cases of diseases associated with PPB will also require registry central pathology review.

3.3.3 Prior Therapy

3.3.3.1 PPB Type I: All patients are eligible and will be followed in the study.

3.3.3.2 PPB Types II or III:

3.3.3.2.1 Types II and III PPB patients without prior Type I PPB diagnosis:
Newly-diagnosed Types II and III PPB patients will be included in the Treatment and Biology Registry.

Prior corticosteroid therapy is allowed.

Patients who have received other chemotherapy regimens or radiation therapy will not be included in the Treatment and Biology Registry.

Patients not included for the Treatment and Biology Registry may be registered for non-study follow-up and are eligible for biology studies.

3.3.3.2.2 Types II and III PPB patients with PRIOR Type I PPB diagnosis:
Types II and III PPB cases which are recurrences of an earlier Type I PPB are included if no chemotherapy was used for the Type I disease.

Patients who have received chemotherapy for Type I PPB may be enrolled for non-study follow-up and are eligible for biology studies.

3.3.3.4 PPB Associated Diseases: All patients are eligible and will be followed in the study.

3.3.4 Informed consent by parent/guardian. (also, where appropriate: assent and HIPPA consent)

4.0 TREATMENT GUIDELINES

Children with PPB should receive care at pediatric oncology specialty centers. Treatment decisions are the responsibility of local institutions. The following are surgery,
chemotherapy, and radiation therapy recommended Guidelines of the Treatment and Biology Registry.

The IPPBR and this protocol do not provide guidelines for treatment of any “PPB Associated Diseases”.
4.1 PPB Biopsy/Surgical Guidelines:

Surgical Principles: (1) Primary resection is preferred, but adequate biopsy (see below) followed by neo-adjuvant chemotherapy and delayed complete resection is acceptable. (2) Complete surgical removal, whether in primary or subsequent surgeries, is highly recommended. (3) Specimens should be submitted fresh to the Pathology Laboratory for molecular studies and snap-freezing for biology studies (see Appendix A-II: 1.2).

4.1.1 Predominantly CYSTIC Lesions (Type I PPB; Type II PPB with minimal solid elements)

4.1.1.1 Anatomic Considerations
Type I PPB is a purely cystic pulmonary/pleural lesion with no gross evidence of cyst-wall thickening or solid nodules suggesting malignancy. Early Type II PPB grossly may appear purely cystic. The clinical and radiographic presentation of Type I and very early Type II PPB are not suspicious for malignancy, and therefore a “cancer operation” is rarely contemplated or performed. Intra-operative pathological examination and frozen sections will rarely indicate the diagnosis. When there is evidence in the patient or family for the PPB Family Tumor Susceptibility Syndrome, a lung cyst should be considered PPB until proven otherwise and a “cancer operation” should be planned.

Type I PPB or early Type II PPB are most often multilocular cysts occurring in the periphery of lung adjacent to and/or involving visceral pleura. The cysts of PPB are usually air filled. Pneumothorax is a common presentation. Radiographically, the lesions are diagnosed as blebs, bullae, “congenital emphysema” or “congenital cystic adenomatoid malformation” (CCAM). These lesions may be 5 – 10 cm in diameter. Rarely these tumors are unilocular cysts and rarely are completely within lung parenchyma. Predominantly cystic PPB may be exophytic and present on the visceral pleural surface, or it may substantially distort or replace lung parenchyma. The cysts may be adjacent to parietal pleura, may lie within lobar fissures and may arise near the lung hilum. Predominantly cystic PPB usually involves one segment or one lobe of the lung, but it may involve a contiguous lobe or may be multifocal and bilateral. Cystic PPB can be highly unsymmetrical, such as very large multilocular cysts in one lobe and scattered small cysts elsewhere. Occasional cystic PPB patients have marked multifocal or bilateral disease making complete resection is impossible; such patients should have the largest cyst(s) removed for diagnostic pathology (see § 4.1.1.2.1.2). In Type I PPB, residual normal lung is typically markedly compressed by cysts or pneumothorax and routinely expands following resection of the diseased lung.

4.1.1.2 Recommended Surgery
This study recommends thoracotomy for predominantly cystic lesions. However, because pre-operative evaluation of predominantly cystic lesions is unlikely to suggest malignancy, thorascopic resections may be undertaken.
4.1.1.2.1 THORACOSCOPIC RESECTIONS

4.1.1.2.1.1 Major Cystic Structures
When thorascopic resection is performed, cystic elements should be removed as completely as possible. Cystectomy is recommended for exophytic tumors. Segmentectomy or lobectomy is recommended to the extent that lung parenchyma is replaced by cyst formation. The cysts are mostly air filled and the specimen is likely to collapse. The resection margin of the specimen should be identified for the pathologist. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.1.2.1.2 Additional Minor Cystic Structures
Some children present because of one large multilocular cyst but also have multifocal cysts involving diverse regions of one or both lungs. These additional cysts are often small (1 – 2 cm diameter). It is not recommended that all such cysts be removed.

4.1.1.2.1.3 Re-operation after Thorascopic Resections
Following thorascopic resection and after pathologic interpretation, an open thoracotomy to achieve a complete resection should be done in two situations:

1. when the tumor is determined to be Type II PPB and the thorascopic resection margin is positive and/or
2. when post-operative CT scan in either Type I or early Type II PPB reveals that portions of a major cystic structure remain.

4.1.1.2.2 THORACOTOMY RESECTIONS

4.1.1.2.2.1 Major Cystic Structures
If open thoracotomy is the initial procedure, cystic elements should be removed as completely as possible. The extent of resection is dictated by the extent of the cystic defacement of lung parenchyma. Cystectomy is recommended for exophytic tumors. Segmentectomy or lobectomy is recommended depending on the extent that lung parenchyma is replaced by cyst formation. The surgical margin should be noted for the pathologist. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.1.2.2.2 Additional Minor Cystic Structures
Some children present because of one large multilocular cyst but also have extensive multifocal cysts involving diverse regions of one or both lungs. These additional cysts are often small (1 – 2 cm diameter). It is not recommended that all such cysts be removed unless they are obvious intra-operatively.

4.1.1.2.2.3 Re-operation after Thoracotomy Resections
If the pathologic diagnosis of predominantly cystic lesions is Type II PPB and the surgical margins are positive, a further open resection is recommended to achieve clear margins.
4.1.2 Predominantly or Completely SOLID Lesions (Types II and III PPB)
4.1.2.1 Anatomic Considerations
Types II and III PPB are thoracic masses either in lung parenchyma or in parietal pleura. Pleural effusion is present in some cases and may be considered empyema; it is rarely cytologically positive and cannot be relied upon for accurate diagnosis.

Type II PPB has gross or microscopic evidence of air-filled epithelial-lined cysts in addition to solid elements.

Type III PPB is entirely solid.

Types II and III PPB usually arise within one lobe of the lung but often invade adjacent structures: another lobe, parietal pleura, diaphragm, chest wall (rare), or mediastinum (rare). They usually destroy the lobe in which they originate. Rarely solid PPB arises in parietal pleura and lung is only compressed. These tumors often fill the hemithorax with marked mediastinal shift. Very rarely, patients require ventilator support until surgery or chemotherapy shrinkage. Tumor measurements of 10 cm x 8 cm x 12 cm are common in children aged 3 - 5 years. Types II and III tumors may be encapsulated but more often have no defining margin. Extensive parietal pleural involvement with studding or sheets of disease occurs. Types II and III PPB may be very necrotic with pre- or intra-operative rupture/spillage. Uninvolved lung may be completely effaced but is usually viable and expands promptly.

Rarely will Types II or III PPB grossly invade major thoracic vessels (as seen in cavoatrial extension of Wilms tumor). Unlike Wilms, PPB may affect right or left circulations with extension to right or left cardiac chambers. Systemic embolization may occur. Any suggestion of vascular involvement (facial plethora, vena cava syndrome, cardiac murmur) should be investigated with vascular ultrasound. Biopsy followed by chemotherapy is recommended for such cases.

4.1.2.2 Recommended Surgery
This study recommends attempted initial tumor resection if it can be accomplished. When this is not deemed possible, open biopsy is recommended. Multiple core needle biopsies may replace open biopsy. Fine-needle aspiration for cytology is not adequate.

4.1.2.2.1 Primary Resection (Recommended)
When predominantly solid PPB is of moderate size, thoracotomy resections are recommended. Lobectomy or bilobectomy is recommended. Pre- or intra-operative rupture/spillage may occur, requiring piecemeal resection. Usually one lobe is unaffected and re-expands. Surgical margins should be sampled and marked for the pathologist. Sites of unresectable residual disease should be titanium clipped for radiographic and possible radiotherapy. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

For very large lesions, pneumonectomy occasionally has been performed.
Major nodular involvement of parietal pleura should be excised. Rarely excision of one or two ribs has been utilized, but chest wall invasion is rare. Diaphragmatic involvement may require excision of a portion of the diaphragm and use of a Gortex patch.

4.1.2.2 Initial Open Biopsy (Recommended)
If resection is not done, adequate biopsy sampling is essential. PPB is characterized by diverse histologic morphologies which must be sampled. Open biopsy should be used. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.2.3 Initial Core Needle Biopsy (Not Preferred)
Adequate biopsy sampling is essential. PPB is characterized by diverse histologic morphologies which must be sampled. If used, multiple core biopsies must be obtained. Fresh tissue should be submitted to the laboratory as a fresh or frozen section and for biology studies.

4.1.2.4 Fine Needle Aspiration Cytology (FNAC) (Not Adequate)
Fine needle aspiration cytology is not adequate.

4.1.2.5 Delayed Resection after Biopsy and Chemotherapy (Recommended)
Although initial biopsy patients receiving chemotherapy may have dramatic tumor reduction, surgical resection is still required. An early chemotherapy response may be transient, and thoracotomy resection should be planned for Week 10, following hematologic recovery after the first three courses of chemotherapy (§ 4.2).

Delayed resection should be as complete as possible following the same guidelines for initial resection described above (§4.1.2.2.1). Tumor margins should be sampled and clipped if questionable for residual disease. Fresh tissue should be submitted to the laboratory to assess chemotherapy effect and for diagnostic and biology studies.

4.1.2.6 “2nd” and “3rd” Look Thoracotomies (Recommended)
For several reasons, strong consideration should be given to surgical control of the primary thoracic disease site:

First, pathology of lesions following neo-adjuvant chemotherapy suggests that anaplastic PPB is less sensitive to chemotherapy than other histologic subtypes. (Anaplasia is common: 75% of Type II PPB and 85% of Type III PPB.12) Therefore chemotherapy alone is unlikely to eradicate PPB.

Second, there are no studies or case reports suggesting that PPB is particularly sensitive to radiation therapy.

Third, sarcoma radiation doses (3,500-4,000 cGy) may be difficult to deliver to some thoracic locations in young children. High doses to residual disease to the chest wall or lateral aspects of the diaphragm may be possible. But, especially because of
anthracycline chemotherapy, high doses to locations along the medial diaphragm, mediastinum and pericardium may not be possible. Wide fields to lung parenchyma must be limited to ~1,800-2,000 cGy and may not be therapeutic for PPB.

Therefore, this study recommends early attempts at surgical control of the primary disease site: at diagnosis or at ~week 10 after three cycles of chemotherapy. See Treatment Schema (§4.2.2).

If disease remains after week 10, consideration should be given to repeat thoracotomy (“3rd look”) and attempted complete resection after 2-3 further courses of chemotherapy. This study recommends up to three thoracotomies to attempt complete resection. Attempted resection times would be approximately Week 0, Week 10, and Week 19. See Treatment Schema (§4.2.2).

4.1.3 Surgery for Metastasis

4.1.3.1 Intracerebral Metastases

Brain parenchyma is the most common metastatic site for PPB. Resection according to general principles of neurosurgery is strongly suggested for intracranial mass lesion(s). Several patients with cerebral PPB metastases have been cured. Because PPB is associated with other dysplastic and neoplastic diseases cerebral disease in a PPB patient cannot be assumed to be PPB. Glioblastoma multiforme, medulloblastoma, and medulloepithelioma have been discovered in PPB children and their kindreds. Cerebrospinal fluid involvement in PPB is very rare.

4.1.3.2 Other Metastatic sites

After brain parenchyma, bone and liver are the most common sites of distant PPB metastasis. Biopsy for diagnosis is recommended, but therapeutic resection is rarely indicated.

Because PPB can be associated with several other dysplastic and neoplastic diseases, sites of new disease in PPB patients cannot be assumed to be PPB and must be investigated. Many PPB children have had additional primary tumors. For example, a child with co-occurring PPB and bladder rhabdomyosarcoma has been observed. Several young women have had ovarian tumors following PPB. Contralateral lung involvement may also represent a second primary disease.

4.2 Chemotherapy Guidelines

Chemotherapy administration, chemotherapy doses, dose modifications for toxicity, and supportive care decisions should conform to local practice guidelines. The following are the recommended Guidelines of this Treatment Registry.
4.2.1 Type I Chemotherapy Decision and Guidelines

Whether to use chemotherapy for Type I PPB is a decision to be made by the patient’s physician and local institution. If the decision is to use chemotherapy, the Treatment and Biology Registry recommended VAC Guideline is as follows:

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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Mesna*:</td>
<td>M*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M*</td>
<td>M*</td>
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<table>
<thead>
<tr>
<th>Week of therapy:</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
<th>32</th>
<th>33</th>
<th>34</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine:</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinomycin D:</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide:</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>Mesna*:</td>
<td>M*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M*</td>
<td>M*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week of therapy:</th>
<th>36</th>
<th>37</th>
<th>38</th>
<th>39</th>
<th>40</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine:</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td>V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actinomycin D:</td>
<td>A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide:</td>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesna*:</td>
<td>M*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution.

Type I roadmaps and hydration guidelines are included in Appendix VIII

#### Recommended VAC Dose Guidelines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>≥ 3 years</td>
<td>1.5 mg/m^2 IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>≥ 1 year and &lt; 3 years</td>
<td>0.05 mg/kg IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 year</td>
<td>0.025 mg/kg IV x 1</td>
</tr>
<tr>
<td>A</td>
<td>≥ 3 year</td>
<td>0.045 mg/kg (maximum dose 2.5 mg) IV X 1</td>
</tr>
<tr>
<td></td>
<td>&lt; 1 year</td>
<td>0.025 mg/kg IV x 1</td>
</tr>
<tr>
<td>C</td>
<td>≥ 3 year</td>
<td>1.2 gm/m^2/dose IV as 1 hr infusion with IV fluids and MESNA, day 0 of weeks 0, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, and 39</td>
</tr>
<tr>
<td></td>
<td>&lt; 3 years</td>
<td>40 mg/kg/dose IV</td>
</tr>
<tr>
<td>M</td>
<td>Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution</td>
<td></td>
</tr>
</tbody>
</table>
### 4.2.2 Types II and III Chemotherapy Guidelines

The Treatment and Biology Registry IVADo regimen guideline for Types II and III PPB is summarized in the following schema:

<table>
<thead>
<tr>
<th><em>Dosing for age &gt; 12 months:</em></th>
<th>I²VADo²</th>
<th>I²VADo²</th>
<th>I²VADo²</th>
<th>I²VADo²</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
<th>IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFO 3 g/m²/d x 1 or 2 d</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VCR 1.5 mg/m²/d x 1 d</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>AMD 1.5 mg/m²/d x 1 d</td>
<td>↓↓</td>
<td>↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DOXO 30 mg/m²/d x 2 d</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>MESNA 600 mg/m²/d x 1 d</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

| Week | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
|------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|

**Recommended radiographic evaluations of chest**
- CXR
- CT

**Recommended surgical intervention**
- #1: Complete resection, if possible.
- #2: at week 10, depending on response. Attempt complete resection if not done at diagnosis.
- #3: at week 19, Attempt a complete resection if not done at #1 and #2.

**Focal radiation therapy, if needed**
- **XRT, if needed (Actino and/or Doxo will be held).**

**Cumulative Doxo: 8 @ 30 mg/M² = 240 mg/M²**

**Initial weekly VCR x 7 doses**

<table>
<thead>
<tr>
<th><em>Dose Modifications:</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR:</td>
</tr>
<tr>
<td>&lt; 6 months</td>
</tr>
<tr>
<td>6 months - 12 months</td>
</tr>
</tbody>
</table>

IVADo roadmaps and hydration guidelines are included in **Appendix IX**
I²VADo² courses (courses #1, #2, #3, #4)

Criteria to start next course: ANC ≥ 750/μL and platelet count ≥ 75,000/μL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>≥ 12 months</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>1 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>0.75 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td>A</td>
<td>≥ 12 months</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>1 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>0.75 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td>I</td>
<td>≥ 12 months</td>
<td>3 g/m²/dose IV over 3 hours on Days 1, 2, (6 g/m²/cycle) with MESNA</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>2 g/m²/dose IV over 3 hours on Days 1, 2, (4 g/m²/cycle) with MESNA</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>1.5 g/m²/dose IV over 3 hours on Days 1, 2, (3 g/m²/cycle) with MESNA</td>
</tr>
<tr>
<td>M</td>
<td>≥ 12 months</td>
<td>600 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>400 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>300 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
<tr>
<td>D</td>
<td>≥ 12 months</td>
<td>30 mg/m²/dose IV over 30 min, Days 1, 2 (60 mg/m²/cycle), If BSA &gt; 2 m², maximum dose 75 mg/day (150 mg/cycle).</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>20 mg/m²/dose IV over 30 min, Days 1, 2 (40 mg/m²/cycle)</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>15 mg/m²/dose IV over 30 min, Days 1, 2 (30 mg/m²/cycle)</td>
</tr>
</tbody>
</table>

* Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. see Appendix A-X: 1.2 for CPM, and Mesna with CPM, doses.
IVA Courses (courses #5 through #12)

Criteria to start each course: ANC ≥ 750/μL and platelet count ≥ 75,000/μL.

IVA Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>≥ 3 years</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>1 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>0.75 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td>A</td>
<td>≥ 3 years</td>
<td>1.5 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>1 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>0.75 mg/m² IV x 1 (maximum dose 2 mg)</td>
</tr>
<tr>
<td>I</td>
<td>*Ifosfamide</td>
<td>Courses 1 - 4: 3 g/m²/dose IV over 3 hours on Days 1, 2, (6 g/m²/cycle) with MESNA Courses 5 - 12: 3 g/m²/dose IV over 3 hours on Day 1 (3 g/m²/cycle) with MESNA Courses 1 - 4: 2 g/m²/dose IV over 3 hours on Days 1, 2, (4 g/m²/cycle) with MESNA Courses 5 - 12: 2 g/m²/dose IV over 3 hours on Day 1 (2 g/m²/cycle) with MESNA Courses 1 - 4: 1.5 g/m²/dose IV over 3 hours on Days 1, 2, (3 g/m²/cycle) with MESNA Courses 5 - 12: 1.5 g/m²/dose IV over 3 hours on Day 1 (1.5 g/m²/cycle) with MESNA</td>
</tr>
<tr>
<td></td>
<td>≥ 1 year</td>
<td>600 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
<tr>
<td></td>
<td>6 – 12 mo of age</td>
<td>400 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
<tr>
<td></td>
<td>&lt; 6 mo of age</td>
<td>300 mg/m²/dose IV with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
</tbody>
</table>

* Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. See Appendix A-X: 1.2 for CPM, and Mesna with CPM, doses.

4.3 Radiation Therapy Guidelines

Although there are no specific studies or case reports specifically supporting a curative role for radiation therapy in PPB radiation therapy should be considered for known, unresectable residual primary disease, after chemotherapy and aggressive attempts at surgical resection. See §4.1.2.2.6

4.3.1 Residual Primary Thoracic Disease

Typical limitations to radiation of lung parenchyma must be followed. Focal boosts to childhood soft-tissue sarcoma doses should be considered where anatomic site allows (e.g., lateral diaphragm or thoracic cage).

The timing of radiation to residual chest disease is suggested in the study schema (§ 4.2.2). Use of radiation is a decision of the treating institution and physicians.

4.3.2 Metastatic Disease

Cerebral Metastasis
Radiation therapy is specifically recommended for control of cerebral metastasis following attempted surgical resection. Several children with cerebral metastases have been cured. Physicians may contact the IPPBR for details of therapy in cured cerebral metastasis cases.
5.0 CHEMOTHERAPY ADMINISTRATION, DOSE MODIFICATIONS FOR TOXICITY, AND SUPPORTIVE CARE GUIDELINES

All aspects of chemotherapy administration (including, for example, hydration, use of uroprotective agents, dose modifications for toxicity, use of hematopoietic stimulants) are the responsibility of the treating physician and institution. Local supportive care practices should be followed.

The following guidelines are included in the appendices:
- **I VII**: Hydration guidelines for Type I PPB
- **Appendix IX**: Hydration guidelines for Types II and III PPB
- **Appendix X**: Dose modifications for toxicity and supportive care guidelines.
- **Appendix XI**: Chemotherapy information for agents used in chemotherapy Guidelines.

6.0 OBSERVATIONS GUIDELINES DURING AND AFTER TREATMENT

Physicians treating PPB and their local institutions will decide the appropriate on- and off-therapy monitoring and surveillance tests, modalities, and schedules. Observation guidelines from the Treatment and Biology Registry are as follows:

### 6.1 Observation Guidelines for Type I PPB

**a) for patients with surgery only**

<table>
<thead>
<tr>
<th>Test-Observation/Time</th>
<th>Diagnosis</th>
<th>Post Surgery/ Baseline</th>
<th>Year 1 after diagnosis</th>
<th>Year 2 after diagnosis</th>
<th>Yearly 3 after diagnosis</th>
<th>Thereafter until age 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx/PE (Ht/Wt), Clinical assessment</td>
<td>X</td>
<td>Monthly</td>
<td>Monthly</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT*</td>
<td>X</td>
<td>X</td>
<td>Every 3 months</td>
<td>Every 3 months</td>
<td>Every 6 months</td>
<td>Every 6 months</td>
</tr>
</tbody>
</table>

*Physicians must recognize that recurrence of chest disease may occur up to 4-5 years after resection of Type I PPB. Furthermore, solid PPB can develop very quickly. It is difficult to perform adequate surveillance for early detection. Modern chest CT scanners with reduced radiation exposures for small children are recommended. Only chest surveillance is recommended. Metastasis has not been observed in Type I PPB.*
b) for patients after chemotherapy, if used

<table>
<thead>
<tr>
<th>Observation</th>
<th>Diagnosis</th>
<th>post surgical baseline, if tumor resected</th>
<th>Week of Therapy</th>
<th>End of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hx/PE, Ht/Wt</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC/Diff/Plt</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urinalysis, Creatinine, SGPT, Alk. Phos, Ca/Phos/Alb, Electrolytes (Na, K, Cl, CO2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest CT (or MRI*)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Abdomen CT or Ultrasound</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Chest MRI: In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in management of Types II and III PPB. For lesions with extensive air-filled cystic components, chest CT is preferred. Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the primary surveillance modality.
6.2 Observation Guidelines for Types II and III PPB

6.2.1 Observation Schedule Types II and III PPB - While on Treatment:

<table>
<thead>
<tr>
<th>Observation</th>
<th>Week 0 Diagnosis</th>
<th>Week 0 post surgical baseline, if tumor resected</th>
<th>Week of Therapy</th>
<th>Week 37</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Course</td>
<td>Week 0</td>
<td>Week 37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx/PE, Ht/Wt</td>
<td>X</td>
<td>1 2 3 4 5 6 7 8 9 10 11 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Diff/Plt</td>
<td>X</td>
<td>X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis, Creatinine, SGPT, Alk. Phos, Ca/Phos/Alb, Electrolytes (Na, K, Cl, CO2)</td>
<td>X</td>
<td>X X X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance or GFR</td>
<td>X</td>
<td>X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td>X</td>
<td>X X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest CT (or MRI*)</td>
<td>X</td>
<td>X X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen CT/Ultrasound</td>
<td>X</td>
<td>X X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X</td>
<td>X X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac ECHO or MUGA and EKG for cardiac monitoring</td>
<td>X</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head MRI or enhanced CT</td>
<td>X</td>
<td>X X X X X X X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Chest MRI: In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in management of Types II and III PPB. For lesions with extensive air-filled cystic components, chest CT is preferred. Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the primary surveillance modality.

6.2.2 Observation Guidelines Types II and III PPB - Post-Therapy:

<table>
<thead>
<tr>
<th>Test-Observation/Time</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Yearly thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hx/PE</td>
<td>monthly</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td>X</td>
</tr>
<tr>
<td>CBC &amp; chemistries</td>
<td>monthly</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>monthly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest &amp; upper abdomen CT (or MRI*)</td>
<td>q 3 mo</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td></td>
</tr>
<tr>
<td>Head MRI or enhanced CT</td>
<td>q 3 mo</td>
<td>q 3 mo</td>
<td>q 6 mo</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td></td>
<td></td>
<td>X</td>
<td>q 5 years</td>
</tr>
</tbody>
</table>

* Chest MRI: In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in management of Types II and III PPB. For lesions with extensive air-filled cystic components, chest CT is preferred. Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the primary surveillance modality.

6.3 Observation Guidelines PPB Associated Diseases

A request for follow-up to the treating institution and or the patient will be sent on a yearly basis.
7.0 PATHOLOGY AND BIOLOGY TISSUE SPECIMENS

REQUESTED SPECIMENS

Preparation of Specimens  See Appendix II

Shipping of specimens

8.0 OFF PROTOCOL AND OFF STUDY CRITERIA

This is a Treatment and Biology Registry. Therefore, a child’s treating physician is responsible for deciding whether to use or to continue to use recommended Guideline therapies.

The Registry will follow outcomes.

9.0 STATISTICS

9.1 Statistical Considerations

The first objective includes estimation of event-free survival (EFS) and overall survival (OS) rates in patients with Type I PPB treated at physician discretion.

The second objective of this study is to estimate EFS and OS rate of patients with Type II/III PPB treated with a prescribed regimen of single-arm chemotherapy.

The third objective is to follow patients with PPB Associated Diseases. A Table with these diseases and other descriptive statistics may be done.

9.1.1 Accrual rate

The IPPBR enrolled 44 patients with PPB in 2007, approximately 85% of which were Type II/III, or 37 per year, with these approximately equally divided between Type II and Type III. Based on these numbers, we expect that a minimum of 30 patients with Type II/III PPB will be eligible for and be enrolled in this study per year.

9.1.2 Endpoints

The primary endpoints for statistical analysis will be time from start treatment to an event, defined as the occurrence of progression or recurrence of PPB, occurrence of a second malignant neoplasm, or death from any cause that is at least possibly related to the original disease or treatment. Secondary endpoints will the best overall response to chemotherapy among patients with radiographically measurable tumor following initial surgery or biopsy, and time to death from any cause.

9.1.3 Statistical methods

Estimates of EFS percent and OS percent will be based on the product-limit (Kaplan Meier) estimate with Greenwood standard errors. Estimates of response rate (CR/PR) will be based on the asymptotic normal approximation to the binomial distribution.
9.1.4 **Accrual target and Statistical Precision**
The accrual goal for this study will be based on achieving sufficient precision for estimating 5-year EFS. Unpublished data from IPPBR in 2006 suggests that 5-year EFS rates in 64 Type II patients and 62 Type III patients are 50% and 32%, respectively, which suggests 5-year EFS for the combined group of ~40%. Assuming a minimum of 2 years follow-up on the last patient enrolled on this study at the time of final analysis and a 5% loss to follow-up rate overall, enrollment of 120 Type II/III patients over 4 years will provide a standard error for the 5-year EFS estimate of approximately ±5.2%. Similar precision will be achieved for the 5-year OS estimate. Precision of EFS and OS estimates in Type I patients and for response in Type II/III patients will depend on the number of Type I patients enrolled and on the number of Type II/III patients with radiographically measurable tumors.

9.2 **Data Management**

9.2.1 **Patient/Tissue Data**
Patient tissue and data will be recorded and maintained by the study office.

9.2.2 **Clinical Data**
Demographic, clinical data, and pathology data will be abstracted into the database using each patient’s unique study identifier number.

10.0 **CRITERIA FOR RESPONSE TO THERAPY**

10.1 **Radiographic Primary Tumor Response, Volumetric:**

10.1.1 **Type I PPB**
The goal for Type I PPB surgery is complete removal of major cystic elements. This must be assessed with early post-operative chest CT scan (see Surgical Guidelines § 4.1) Small and multifocal cysts cannot all be resected; if major cystic elements are bilateral, bilateral surgery is recommended.

Complete Response/Resection (CR) for Type I PPB is radiographic evidence of removal of all major cystic elements.

Partial response/resection (PR): residual elements of major cystic structures larger than 10% volume of initial cystic volume.

Progressive Disease (PD): At least 40% cyst volume increase compared to the smallest volume obtained since the beginning of therapy.

10.1.2 **Types II and III PPB**
For Type II and III PPB patients treated with primary surgery or with neoadjuvant chemotherapy and surgery: three-dimension, volumetric measurements are required to measure chemotherapy response. CT and/or MRI are reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest.

- Complete Response (CR): Complete disappearance of the tumor-
Depending on therapy sequence, CR can be achieved in five ways:

1. following neoadjuvant chemo. (unusual)
2. following neoadjuvant chemo and delayed primary surgery. (usual)
3. following neoadjuvant chemo, surgery, and requiring adjuvant chemo. (unusual)
4. following primary surgical resection. (usual)
5. following primary surgical resection and adjuvant chemo. (usual)

The way in which CR is achieved will be considered in outcome evaluations.

- Partial Response (PR): At least 65% volume decrease compared to the measurement obtained at diagnosis. This is the minimum tumor volume (maximal response to all therapies) achieved at any time after diagnosis. As in the CR criterion above, any of the above therapy sequences may result in this PR assessment.

- Progressive Disease (PD): At least 40% tumor volume increase compared to the smallest volume obtained since the beginning of therapy.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as a reference the smallest disease volume since treatment started. Assessments which meet these criteria must be >6 weeks apart.

- Neoadjuvant Chemotherapy Response: for children treated with neoadjuvant chemotherapy, the maximal volume decrease before surgical resection will be determined and considered in outcome evaluations.

10.2 Metastatic Disease Response Measurements

Metastatic disease at diagnosis in PPB is rare (~ 5 cases among 250 IPPBR pathology-reviewed cases. IPPBR unpublished data). Responses of metastatic disease at diagnosis will be tabulated and evaluated individually (for example: number of bone lesions and response to chemotherapy and/or radiation).

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Adverse Event Reporting Purpose

Adverse reporting, as required by regulatory agencies, must meet the specific guidelines of the country where each individual subject is enrolled. Data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2 Determination of Reporting Requirements

Adverse events reporting should be first and foremost follow the guideline of the local institution or country/state requirements.
We encourage notification to the Registry adverse events for any of the agents used in this Treatment Registry, all of which are commercially available agents. Notification should include:

1) The characteristics of the adverse event including the grade (severity).
2) The relationship to the study therapy (attribution).
3) The prior experience (expectedness) of the adverse event.

Determine the prior experience. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current Agent-Specific Adverse Event List (provided in the Drug Information Appendix XI of this protocol); or
- the drug package insert.

The procedures described below should be followed.

11.3 Reporting of Adverse Events for Commercial Agents:

Commercial reporting requirements are provided below in Table A. The commercial agent(s) used in this Registry are listed in the Drug Information Appendix XI.

Table A

Reporting requirements for adverse events experienced by patients on this Treatment Registry.

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected</td>
<td>Expected</td>
</tr>
<tr>
<td>Unrelated or Unlikely</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>Registry Adverse Events Report Required</td>
<td>Registry Adverse Events Report Required</td>
</tr>
</tbody>
</table>

This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported to via a Registry Adverse Events Report form.

11.4 Reporting Secondary AML/MDS

Although this Treatment Registry is not an NCI sponsored trial, the IPPBR requests that participants use NCI-similar procedures to report all cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on this Treatment Registry.

Submit the following information within thirty days of an AML/MDS diagnosis occurring after treatment:
37

· a completed PPB Registry Secondary AML/MDS Report Form (Appendix XI).
· a copy of the pathology report confirming the AML/MDS; and
· a copy of the cytogenetics report (if available).

Submit the information via fax to:

The International PPB Study Office
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave S, Suite 412
Minneapolis, MN 55404, USA
Tel: (612) 813-7115
Fax (612) 813-7108
E-mail: gretchen.williams@childrensmn.org

12.0 RECORDS AND REPORTING

12.1 Data Submission

The following data will be provided on every enrolled patient.
(Records may be de-identified at the local institution, replacing all unique identifiers with the Patient Unique Study Identification Number. If records are not de-identified locally, they will be de-identified at the Treatment and Biology Registry Office.)

- Signed study consent (and assent if required) and HIPAA if USA patient
- Human Subjects Committee, Institutional Review Board or Helsinki Committee study approval letter (if applicable at the patient’s institution)
- Hospital discharge summaries
- Pathology reports on
  o surgical specimens (biopsy, resection, and metastasis)
  o pleural fluid cytology
  o bone marrow
  o spinal fluid
  o molecular studies
  o cytogenetic studies
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc)
- Digital copies of diagnostic studies (and of selected follow-up studies, when requested)
- Treatment records (chemotherapy, radiation therapy, including chemotherapy roadmaps or Case Report Forms:
  Type I PPB VAC roadmaps: Appendix VIII
  Types II/III PPB IVADO roadmaps: Appendix IX
  Case Report Forms: Appendix XIII
- Oncology clinic records
- Consultations
- Family medical history including family medical history diagram
12.1.2 Submission Address
(for Pathology Central Review shipment See Appendix A-II: 1.4; for biologic material shipment, see Appendix A-II: 1.5).

Send data to the Treatment and Biology Registry Office:

The International PPB Study Office
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave S, Suite 412
Minneapolis, MN 55404, USA

Tel: (612) 813-7115
Fax (612) 813-7108
E-mail: gretchen.williams@childrensmn.org

13.0 IMAGING STUDIES

See § 6.1 for Type I PPB and § 6.2 for Types II/III PPB “Treatment and Biology Registry Observation Schedule”

13.1 Primary Site Imaging

For Type I PPB, chest CT is the preferred method of primary site imaging.

For Types II and III PPB, chest CT versus chest MRI should be considered. For serial assessments of response, the same modality of primary site imaging should be used. In general, MRI has limited value in the chest. However, for delineating sarcomatous PPB from other soft tissues in the thorax, for following response to chemotherapy, and for reducing diagnostic radiation exposure, thoracic MRI can be useful in Types II and III PPB. MRI may require more sedation and may be more costly. For Type II lesions with extensive air-filled cystic components, chest CT is preferred.

Because additional air-filled pulmonary cysts can develop or enlarge in children with PPB, chest CT should be done at least annually when MRI is the surveillance modality for the primary tumor.

The primary tumor should be measured and reported in three dimensions.

13.2 Metastatic Site Imaging

Suggested techniques for imaging metastatic sites is as follows:

- Brain parenchyma: MRI (preferred); enhanced CT (acceptable)
- Bone: radionuclide bone scan for screening, plain radiographs for questionable areas on bone scan
- Liver: abdominal CT with and without contrast or ultrasound
**APPENDIX I: INTERNATIONAL PPB REGISTRY PRE-TREATMENT (POST SURG; POST PATH)**

**STS-STYLE GROUP CLASSIFICATIONS**

<table>
<thead>
<tr>
<th>&quot;STS Clinical Group&quot; Post Surg and Path</th>
<th>PPB Type</th>
<th>Tumor Site Extension/Invasion (if T1 or T2, add modifier)</th>
<th>Size*</th>
<th>Intrathoracic/ Hilar Nodes* (add modifier)</th>
<th>Metastasis</th>
<th>Laterality</th>
<th>Focality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia or b, ila or b, ilia or b</td>
<td>I</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0</td>
<td>M0</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
<tr>
<td>(In Type I PPB; subgroups lb and IIb probably do not exist)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ia or b, ila or b, ilia or b</td>
<td>II</td>
<td>TX, T1, or T2</td>
<td>a, b or c</td>
<td>N0, N1, NX</td>
<td>M0</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
<tr>
<td>Ia or b, ila or b, ilia or b</td>
<td>III</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0, N1, NX</td>
<td>M0</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
<tr>
<td>IV</td>
<td>II or III</td>
<td>TX, T1 or T2</td>
<td>a, b or c</td>
<td>N0, N1, NX</td>
<td>M1</td>
<td>u, b</td>
<td>u, m, fx</td>
</tr>
</tbody>
</table>

**Group I:** Localized disease, completely resected (documented clear margins preferred)
- (a) confined to lobe (and associated visceral pleura) of origin or to parietal pleura
- (b) contiguous involvement (infiltration to adjacent lobe, diaphragm, mediastinum, parietal pleura, or chest wall beyond pleura).

**Group II:** Gross total resection (GTR) with microscopic residual
- (a) GTR, micro residual, and no known intrathoracic/hilar node involvement
- (b) GTR, micro residual and path pos intrathoracic/hilar nodes

**Group III:** Incomplete resection with gross residual disease Biopsy or incomplete resection with macroscopic residual
- (a) biopsy only
- (b) gross/macro residual but >50% resection

**Group IV:** Metastatic disease

**Abbreviations:****
- vp = visceral pleura
- pp = parietal pleura
- TX: T status uncertain
- T1: "Confined to anatomic site of origin" = confined to tissue of origin
- T1l: confined to vp + lobe of origin
- T1pp: confined to pp of chest wall, mediastinum, or diaphragm
- T2: "extension and/or fixation to surrounding tissue" = extends beyond lobe/vp of origin to another lobe or to adjacent intrathoracic structures:
- T2l: invades another lobe/vp of the lung;
- T2d: invades diaphragm or assoc pp;
- T2cw: invades chest wall or assoc pp;
- T2m: invades mediastinum or assoc pp
- T2: does not include very light adhesions between lobes or between lobes and parietal pleura
- T2 may involve more than one surrounding structures; code all.
- Maximum diameter*:
  - (a) < 5 cm.
  - (b) 5 - 10 cm.
  - (c) > 10 cm.
- N0: ns; not clinically** involved, not sampled
- N1: ns: clinically involved, sampled, path -
- N1, sp+: clinically involved, sampled, path +
- NX: status unknown/not assessed, not mentioned
- M0: no distant metastasis
- M1: distant metastasis*
- Laterality of lung cysts and/or solid lesions:
  - u: unilateral
  - b: bilateral
  - m: multifocal
  - fx: focality not determined

*max diam of: cyst, or cyst + tumor, or tumor (size does not include pneumothorax)
*supraclavicular or infraabdominal nodes are distant metastasis
"clinically" = noted by radiography or by surgeon at operation

---

*supraclavicular or infraabdominal nodes are distant metastasis
"clinically" = noted by radiography or by surgeon at operation
*any nodes outside the thoracic cavity are distant mets

m = multifocal: discrete separate cysts and/or PPB within one or more lobes. (If bilateral, may be multifocal on one side and unifocal on other.)

u = unifocal: solitary lesion
fx = focality unknown or undetermined (large lesions often obscure residual lung detail)
APPENDIX II: PATHOLOGY AND BIOLOGIC TISSUE SPECIMENS

DNA derived from tumor, normal lung, will be appropriately stored indefinitely for future research.

A-II: 1.1 Tissue for Diagnosis - Preparation

A-II:1.1.1 Histologic Sampling

1. Incisional biopsy or core needle biopsy – If primary resection is not used, incisional biopsy is recommended. If core needle biopsies are used, several cores should be taken to obtain sufficient tissue is for diagnosis and for biology studies. Fine needle aspiration cytology (FNA) is not acceptable.

2. Tumor excision – Representative tissue from all the varying regions of the tumor mass must be sampled for classification. Adequate sampling requires approximately 1 section per cm diameter of tumor. Include samples of both cystic and solid areas if both are present. Tissue sampling should focus on viable appearing tissue. Tissue margins should be examined histologically to evaluate complete or incomplete tumor resection when applicable.

Consider preserving additional tumor tissue – fresh, snap frozen, paraffin or formalin blocks for the PPB Biology Specimens Reference Bank (§ A-V: 1.3).

A-II: 1.1.3 Recommended Histologic and Microscopic Studies

PPB is a pattern diagnosis made with routine histopathologic and immunologic stains. Microscopically, Type III PPB and the solid areas of Type II PPB show at least one of four basic histologic patterns that may blend into each other: (1) cohesive aggregates of primitive small cells with hyperchromatic nuclei, high ratio of nuclei to cytoplasm, and brisk mitoses resembling the blastema of a Wilms tumor; (2) spindled, stellate, and small ovoid cells in a variably prominent myxoid stroma resembling embryonal rhabdomyosarcoma; (3) spindle cell sarcoma resembling synovial sarcoma of congenital-infantile fibrosarcoma; or (4) nodules of immature or overtly malignant cartilage. Individual or groupings of large anaplastic cells with highly atypical mitotic figures are present in 75% of Type II and 85% of Type III cases. Eosinophilic hyaline bodies are often seen in association with anaplastic cells. Within any one tumor, not all patterns are equally represented and one or two patterns may dominate the overall microscopic appearance. Occasional cases show other sarcomatous subtypes. Rarely neuroblastic differentiation has been seen.

A-II: 1.1.3 PPB Tumor “Type” Classification

PPB tumors will be classified as Type I, Type II and Type III according to the criteria supplied Background (§ 2.2) and Pathology Diagnosis (§ 2.2.4) sections.

Pathologists are advised that Type II and especially Type III PPB can be necrotic with
“cysts” not lined by respiratory epithelium. These are “pseudocysts” and do not represent the pulmonary cyst remnants necessary for Type II PPB classification.

**A-II: 1.2 Tissue for Biology Studies – Preparation**

Specimens from the Pathology Laboratory requested for Biology Studies include, when available:

- Fresh and frozen tumor tissue (and, when present, normal tissue)
  AND
- Paraffin-embedded tumor tissue (and, when present, normal tissue)
  AND/OR
- Formalin-fixed tumor tissue (and, when present, normal tissue)

**A-II: 1.2.1 Preparation of Snap Frozen Primary or Metastatic Tumor and Normal Tissue**

Prepare frozen specimens of tumor and non-neoplastic lung or other tissue for Biology Studies as follows:

From several areas of viable tumor, prepare 1 cm³ (1 gram) aliquots of tumor and normal tissue (up to 10 samples if available), wrap in foil and snap freeze in liquid nitrogen or cold isopentane.

Place in a sealable plastic bag and label bag:

(a) with the patient’s unique study identifier number
(b) surgical pathology number
(c) “tumor” versus “normal”
(d) tissue site
(e) date obtained

Store in a manner that will preserve the nucleic acids in the specimen (-70 to 80 °C freezer or liquid nitrogen tank). Specimens must be kept below -70° C until shipped. A regular freezer (-20° C) is not adequate. See shipping instructions in § A-II: 1.4.

**A-II: 1.2.2 Preparation of Paraffin-embedded Primary or Metastatic Tumor and Normal Tissue**

When sufficient paraffin-embedded tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue is useful for Biology Studies.

Place the blocks in paper envelopes and label envelopes:
(a) with the patient’s unique study identifier number  
(b) surgical pathology number  
(c) “tumor” versus “normal”  
(d) tissue site  
(e) date obtained

See shipping instructions in § A-II: 1.4.

**A-II: 1.2.3 Preparation of Formalin-fixed Primary or Metastatic Tumor and Normal Tissue**

When sufficient formalin-fixed tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue is useful for Biology Studies.

"Cassette-sized” aliquots of tumor and adjacent normal tissue (when available) should be placed in appropriately-labeled formalin jars. Stretch the Parafilm around the jar lids after the lids are attached to the jars. Using a waterproof marker, label the jars:

(a) with the patient’s unique study identifier number  
(b) surgical pathology number  
(c) “tumor” versus “normal”  
(d) tissue site  
(e) date obtained

These should be shipped as soon as convenient since excessive fixation reduces the usefulness of the tissue. See shipping instructions in § A-II: 1.4.

**A-II: 1.3 Biology Studies - Specimens Requested**

**A-II: 1.3.1 Preserved tissue for Biology Studies**

**A-II: 1.3.1.1 Paraffin-embedded tissue** (primary or metastatic tumor or normal tissue)

When sufficient paraffin-embedded tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue will be submitted for Biology Studies.

See shipping instructions in § A-II: 1.5.

**Formalin-fixed tissue** (primary or metastatic tumor or normal tissue)

When sufficient formalin-fixed tissue has been dedicated to diagnostic studies, excess primary tumor, metastatic tumor or resected normal tissue will be submitted for Biology Studies.

See shipping instructions in § A-II: 1.5.
**Frozen tumor tissue** (and, when present, normal tissue). See shipping instructions in § A-II: 1.5.

**Fresh tumor tissue** (and, when present, normal tissue). Contact PPB Registry pathologist Dr. D. Ashley Hill (ph: 202-476-2815; email: dashill@cnmc.org) for instructions.

### A-II: 1.4 Shipment of Specimens for Central Pathology Review
(Required for Treatment and Biology Registry enrollment)

Treatment and Biology Registry enrollment is based on local pathology diagnosis. However, pathology material and pathology reports are sent to the Treatment and Biology Registry Office for central pathology review. Any discrepancies in the diagnostic interpretation will be discussed directly with the submitting pathologist or clinician. If the central-review diagnosis is not considered PPB, the referring physician will be notified promptly. Cases which are not PPB will be removed from the study unless the diagnosis makes the case eligible for the Associated Diseases arm of the Registry.

**Required materials:**
- Label all materials with the patient’s unique study identifier number.
- Call or email the Study Office (612 813 7115 or gretchen.williams@childrensmn.org) to notify the study of the shipment. Shipping account number is available to cover shipping cost.
  - (A) 1 H&E section of all available blocks, and
  - (B) 1 or 2 representative paraffin blocks from excess tumor tissue
  - OR
  - (C) Prepare from 2 representative paraffin blocks:
    - 2 H&E slides from the same blocks and
    - 10 unstained sections (on plus-charged, polarized slides) for immunoperoxidase studies,

Include with the blocks or slides:
1. Institutional Pathology Report
2. Institutional Operative Report
3. Study Specimen Transmittal Form
4. Gross photographs are encouraged (digital format preferred)

**Send all central pathology review materials to:**

International PPB Registry
Children's Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
A-II: 1.5 **Shipment of Biologic Specimens**

(Requested)

Biologic specimens requested in this study include, when available:

- Fresh or frozen tumor tissue (and, when present, adjacent normal tissue) from biopsy, resection and/or metastasis
- Paraffin-embedded tumor tissue (and, when present, adjacent normal tissue) from biopsy, resection and/or metastasis
- Formalin-fixed tumor tissue (and, when present, adjacent normal tissue) from biopsy, resection and/or metastasis

**NOTE:** All shipments MUST be arranged in advance to ensure delivery on weekdays and preservation of tissue during transit. All necessary collection containers, shipping materials, address labels, biohazard labels, and courier billing forms will be provided by the Study. Fresh, frozen tissue samples, Pathology blocks or slides do not need to be packaged or shipped together.

To obtain collection and shipping materials, or to schedule shipments, contact the Study Office:

Phone: 612 813 7115
Email: gretchen.williams@childrensmn.org
Fax: 612 813 7108
APPENDIX III: STUDY ENROLLMENT AND PATIENT ELIGIBILITY

- An institution, perhaps with a coordinating cooperative oncology group, approves this Treatment and Biology Registry in advance of a particular child’s diagnosis. This may include approval of therapy guidelines offered by the Registry. If a child with PPB is diagnosed in such an institution, parental consent for Registry enrollment is obtained and therapy is initiated. Medical records and/or biologic specimens are sent to the Registry.

- A child is diagnosed with PPB. Because of its rarity, the institution has not approved in advance therapy for or study of PPB. The institution decides upon and initiates the child’s therapy. The institution decides whether to participate in the Treatment and Biology Registry. The institution obtains all regulatory approval to participate and enroll patients on the Treatment and Biology Registry. Parental consent for Registry enrollment is obtained. Medical records and/or biologic specimens are sent to the Registry.

- A child is diagnosed with PPB. Because of its rarity, the institution has not approved in advance therapy for or study of PPB. The institution decides upon and initiates the child’s therapy. The institution allows the parents to act independently and to agree directly with the Treatment and Biology Registry to share their child’s medical record and/or to provide biologic specimens. The institution complies with the parents’ wishes.

- The above study enrollment and eligibility steps are also followed for individuals diagnosed with a condition associated with PPB.
APPENDIX IV: NON-CHILDREN’S HOSPITALS AND CLINICS
OF MINNESOTA INSTITUTION CONSENTING DOCUMENTS,
SAMPLE CONSENTING DOCUMENTS, AND SPANISH
CONSENTS
Appendix IV – A: Non-Children’s Hospitals and Clinics of Minnesota Institutions: Type I PPB - Consenting Documents

Appendix IV – B: Non-Children’s Hospitals and Clinics of Minnesota Institutions: Type Types II and III PPB - Consenting Documents

Appendix IV – C: Type I PPB - Sample Consenting Documents

Appendix IV – D: Types II and III PPB - Sample Consenting Documents

Appendix IV – E: Non-Children’s Hospitals and Clinics of Minnesota Institutions: Types II and III PPB - Spanish Consents

Appendix IV – F: Non-Children’s Hospitals and Clinics of Minnesota Institutions: Types II and III PPB - Spanish Consents
Appendix IV – A: Non-Children’s Hospitals and Clinics of Minnesota Institutions: Type I PPB - Consenting Documents
Type I PPB - Informed Consent

International PPB Treatment and Biology Registry

_____________________________
Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry

PPB Treatment and Biology Registry Office
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN  55404   USA

RESEARCH CONSENT FORM –Type I PPB

INTRODUCTION
You are being asked to participate in a childhood cancer research study called a Treatment and Biology Registry; it is for children with the rare childhood lung tumor called pleuropulmonary blastoma (PPB). A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue and saliva or blood) from patients with PPB and from their parents. To participate, your agreement is necessary, but it is your choice. You are being asked to participate because your child has been diagnosed with Type I PPB.

- If you are a parent or legal guardian of a child who may be included in this Treatment and Biology Registry, your permission is required for your child to be included.

- If you are a Type I PPB patient and are old enough to consent to treatment without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.

- Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (usually ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

Part 1: Collecting data on children with Type I PPB (“cystic PPB”) and on their treatment. Children diagnosed with Type I PPB will be treated according to decisions at their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

Part 2: The second part of this study involves research into the biology of PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens of the lung cyst (cystic tumor) and saliva and/or blood specimens for biological research.

Your doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only...
people who choose to take part. Please take your time to make your decision about taking part. You may
discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your
health care team. If you have any questions, you can ask your doctor or members of the Registry staff for
more explanation.

This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from
many countries. The research is coordinated by The International PPB Registry based at Children's
Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and
Children's Hospitals of Washington University, St Louis, Missouri USA; and Children’s National
Medical Center, Washington, D. C., USA.

WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?
You are being asked to take part in this study because your child has a rare malignant (cancerous) tumor
called Type I pleuropulmonary blastoma (Type I PPB, also called cystic PPB).

1. What is PPB and Type I PPB? PPB is a very rare tumor. It arises in tissue called “pleura” (pleura
covers the inside of the chest cavity and also covers the surface of the lung); PPB can also arise in the
“pulmonary” tissue, which is the lung itself. PPB is usually a cancer of young children, under age 72
months, but it may occur in older children. PPB is not related to the lung cancers which occur in adults.

There are three types of PPB: Types I, II, and III PPB. Type I PPB is a cyst in the chest. On x-rays, the
cysts of Type I PPB look like benign (non-cancerous) lung cysts of young children called “CCAM” or
“CPAM”, which your doctor can explain to you. Type I PPB is diagnosed under the microscope after a
cyst is surgically removed. Type I PPB is malignant; it is an early malignancy which is usually cured. If
Type I PPB is not cured while it is Type I, it can progress to the much more serious forms of PPB called
Type II and Type III PPB. There are no known instances of Type I PPB spreading to other parts of the
body.

2. Treatment of Type I PPB: Children with Type I PPB require surgery to remove the lung cyst as
completely as possible. After surgery, there are different opinions about whether more treatment
(chemotherapy; anti-cancer drug therapy) is useful to cure children. Some pediatric cancer doctors choose
to use chemotherapy for Type I PPB; some choose not to use it. The reason doctors do not “know” what
is best for Type I PPB is that it is so rare. No large group of children with Type I PPB has ever been
collected together to determine what treatments work best.

This research study suggests surgery as complete as possible for Type I PPB. Then your child’s doctor
will decide whether to recommend chemotherapy. If your child’s doctor does recommend chemotherapy,
he or she may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry,
but there is no information to judge whether this guideline is better than other chemotherapy your doctor
may choose.

This Registry will collect information about how Type I PPB cases are treated. After enough cases have
been collected and enough time has passed to learn how the children have done, the results will be made
available to help doctors learn what therapies may be helpful for Type I PPB.

3. PPB Biology and Genetics: In 30-40% of cases, children with PPB or their family members have
other medical conditions. One of these conditions is lung cysts which may develop into serious cancers.
The evolution of lung cysts into serious solid tumors and to certain illnesses is called the “biology of
PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes
some family members to PPB or other conditions and may be passed from generation to generation. A
mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB cases have this mutation and how it may cause the disease.

The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.

WHAT DOES THE TREATMENT AND BIOLOGY REGISTRY INVOLVE?
Study Part 1: Collection of Data on Treatment of Type I PPB:
There are three major ways to treat cancer and PPB:

- **Surgery** to remove cancer tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells.
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells.

Surgery is necessary for Type I PPB. It is not known whether chemotherapy for Type I PPB improves the chance for cure; some doctors recommend chemotherapy; other doctors do not. Your doctor and his or her colleagues will decide whether to recommend chemotherapy for your child. Radiation therapy is not used for Type I PPB.

This research will collect information on how children with Type I PPB are treated and what is their outcome.

Study Part 2: Research into PPB Biology and Genetics:

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB. This study asks for permission to collect family medical history information, to store excess portions of the child’s Type I PPB tumor (cyst), and to collect and store saliva or blood from the child, from the mother and from the father for research uses.

WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?
Study Part 1: Type I PPB is very rare and there is no established “standard” or “best” therapy. Surgery is necessary. After that, there is not enough information to know whether chemotherapy cures more children than surgery alone would do. The goal of this research study is to collect information on how Type I PPB is treated and analyze the information to see whether the use of chemotherapy after surgery helps cure more children.

Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from PPB patients and their parents for research to try to answer some of these questions.

In summary, the goals of this Treatment and Biology Registry are:

1) To collect data on treatment of Type I PPB and to learn the success rates of different treatments.

2) To collect family medical histories and to collect and save Type I PPB cyst samples and saliva or blood samples from the PPB child and from the mother and father in order to learn more about the biology of PPB and genetic factors in PPB.
HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
We estimate that about 20-30 Type I PPB patients per year from around the world will be collected in this Registry.

WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?
Study Part 1. Treatment of Type I PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: how much surgery and whether to use chemotherapy. This research will collect information about your child and on how the Type I PPB was treated. This also involves collecting x-rays and tissue from surgery to review and confirm the diagnosis of Type I PPB.

Study Part 2. Biology and Genetics of PPB: The biology and genetic studies of this research involve the following biological samples:

- From the child with PPB:
  - After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies.
  - Collecting blood or saliva for DNA samples for research studies.

- From the Mother:
  - Collecting blood or saliva for DNA samples for research studies.

- From the Father:
  - Collecting blood or saliva for DNA samples for research studies.

In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.

HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?
Your child will be followed indefinitely in order to determine the outcome of the Type I PPB.

PPB cyst tissue from the time of initial surgery will be saved indefinitely to be used for research into causes and treatment of PPB. Blood or saliva samples from your child and from the mother and father will also be saved indefinitely for research into causes, biology, and treatment of PPB.

CAN MY CHILD STOP BEING IN THIS TREATMENT AND BIOLOGY REGISTRY?
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)
WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child's medical data in the Registry will help physicians and researchers learn more about PPB and its treatment. The information may be helpful in the treatment of PPB in the future. Also, study of biologic specimens in this Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat PPB more successfully.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of Type I PPB patients for evaluation of the results of their treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or hospital.

HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?
When a childhood cancer research study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with PPB are to be treated (your child’s doctor and his or her colleagues make those decisions), so it is not mandatory that this Registry has been reviewed and approved at your child’s hospital. Even though it may not be mandatory, some hospitals do choose to formally review a project like this.

This PPB Treatment and Biology Registry project has been approved at the children’s hospitals in Minnesota, Missouri, and Washington, D.C. who are coordinating the research.

Regardless of whether your child’s doctor and hospital have specifically approved this research project, your consent to participate is required. Many institutions encourage parents to consider participation in Registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If
information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.

The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.

WHAT ARE THE COSTS OF TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?
There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?
Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at your local hospital will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS REGISTRY?
You can talk to your local doctor about any questions or concerns you have about this research. Your physician may direct you to a local Research or Ethics Board administrator at your hospital who can also help you. You may also choose to discuss participation with support personnel at your child’s hospital, such as social workers or family support counselors.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org). You may also call the Institutional Review Board Administrator at Children’s Hospitals and Clinics of Minnesota at (612) 813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES

You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

**Part 1: Collection of Information on Type I PPB Treatment**

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I agree to have my child be a part of the Treatment and Biology Registry Part 1: Collection of Information on Type I PPB Treatment.

**PATIENT’S NAME ________________________________**

*Printed*

Parent/legal guardian ____________________________  ____________________________

*Print name           Signature*

Relationship to patient: __________________ DATE __________________

Please also answer this question:

Researchers studying PPB would like your permission to be able to contact you in the future if new PPB research topics are identified for which your participation would be helpful.

**Do you agree to be contacted in the future about additional, special PPB research studies?**  (You do not need to agree to this.)

_____ I agree to be contacted in the future      _____ I do not agree to be contacted in the future

**IF YOU AGREE:**

Name: ____________________________

Address: ____________________________

City, State, Postal/Zip Code: ____________________________

Telephone Number: ____________________________

Email address: ____________________________

IRB#: 0909-082  Initial IRB Approval: 12/22/2009

Most recent IRB approval: 07/22/2015
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB and possible genetic factors which may be responsible for some cases of PPB. These research activities are separate from collecting data on how Type I PPB is treated.

We ask that the PPB patient and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the collection of Type I PPB Treatment, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in biology studies without taking part in Part 1 on Type I PPB Treatment.)

WHAT DOES THIS PPB BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:

1. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.
2. To save leftover PPB cyst tissue (if available) from your child’s surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies.
3. To collect and save saliva or blood samples from your child and from each biological parent for research.

The amount of saliva collected will be about 2 tablespoons (30 ml) and the amount of blood will be about 2 teaspoons (10 ml). In most cases, saliva will be collected. PPB cyst tissue will be taken from the cyst removed at surgery after all diagnostic requirements are satisfied.

Specimens saved in this Biology Registry will be used to learn many details about PPB cancer cells and any normal cells that might surround the cancer cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how the cancer is different from normal tissue. DNA from saliva or blood or tumor tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s cyst tissue and your child’s and your saliva or blood specimens will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for research into familial patterns of PPB and related diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this Treatment and Biology Registry.
Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

**HOW LONG WILL SPECIMENS BE SAVED FOR BIOLOGY RESEARCH?**

Tumor tissue, saliva or blood specimens, and family medical histories will be saved indefinitely.

**CAN MY CHILD OR I STOP BEING PART OF THIS BIOLOGY REGISTRY?**

Yes. You can inform the Treatment and Biology Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

**ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS BIOLOGY RESEARCH?**

You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB. It is possible that your child’s doctor or hospital is doing some biology research on tumors and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

**ARE THERE ANY BENEFITS?**

There is no direct benefit to you or your child from participating in the PPB Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.

**ARE THERE ANY RISKS?**

The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private. Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.
WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?
If you have any questions, please talk to your doctor or other patient support personnel at your child’s hospital.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org). You may also call the Institutional Review Board Administrator at Children’s Hospitals and Clinics of Minnesota at (612) 813-7646 in Minneapolis, Minnesota USA.

A document called "How is Tissue Used for Research?" is attached to this consent form.

MAKING YOUR CHOICE ABOUT PARTICIPATING IN PPB BIOLOGY REGISTRY
One parent can authorize participation of a child in Part 2: the PPB Biology Research Registry. For the parents to take part, the patient’s mother must authorize her own participation and the patient’s father must authorize his own participation. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s PPB care.

After reading each sentence, circle "Yes" or "No" and write your signature and date in the spaces provided.

Consent for Participation in PPB Biology Registry Research:
Family Medical History and Saving Cyst Tissue and Saliva or Blood for Research

1. Your Child’s Participation in PPB Biology Registry
I agree to allow my child’s family medical history to be collected. I also agree to allow saliva or blood samples from my child to be collected and saved and to allow any leftover PPB cyst tissue (if available) from my child to be saved for research studies related to PPB.

Yes  No  _________________________  __________________
Signature of parent/guardian  relationship to patient

____________________
Date

2. PPB Patient’s MOTHER’S Participation in PPB Biology Registry
I agree to allow my family medical history to be collected. I also agree to allow my saliva or blood samples to be collected and saved for research studies related to PPB.

Yes  No   ____________________________    _____________________
Signature of MOTHER          Date

3. PPB Patient’s FATHER’S Participation in PPB Biology Registry
I agree to allow my family medical history to be collected. I also agree to allow my saliva or blood samples to be collected and saved for research studies related to PPB.

Yes  No   ____________________________   _____________________
Signature of FATHER            Date

IRB#: 0909-082
Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
Type I PPB Informed Assent for Participation in The International PPB Treatment and Biology Registry

Name: ____________________________

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Study Office:
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN 55404 USA

Assent Form for Child or Adolescent Ages 7-17 with Type I PPB

We are asking you to take part in a research study because you have pleuropulmonary blastoma (PPB). PPB is a rare type of cancer in the lung. A research study is when doctors work together to try out new ways to help people who are sick. In this study, wants to learn more about PPB and how to treat it. We will do this by collecting records on how doctors treat children with Type I PPB. Based on past experiences, the Registry makes suggestions on how PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want to include you as well. Children and teens with Type I PPB who are part of this study may be treated with surgery and chemotherapy. Your doctor will decide whether to recommend this to your parents and will discuss it with them and you. Chemotherapy is a type of strong medicine that destroys cancer cells. Chemotherapy can also cause side effects that could make you temporarily feel sicker.

As part of a study, information about your illness and your surgery and other possible treatments is sent to the main PPB Study research office. Doctors from around the world want to share information about treating children and teenagers who have Type I PPB. By sharing information, we can more quickly learn the best ways to treat cancer. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also send receive a sample of the cyst that was removed from your chest so that they can learn in the future about how and perhaps why PPB cancers exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it. We will also ask for a sample of saliva, and maybe a small tube of blood, from you to store for future research into why some people have PPB.

Your mother or father or guardian can help you decide whether to agree to this scientific study. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.
Please answer the following questions by circling either YES or NO and entering your initials.

1. My tissue and saliva or blood may be sent to the PPB Study office to be used in research about PPB.
   
   YES  NO  Initials _______

2. My leftover tissue, blood, or saliva may be kept by the PPB Study office for use in future research studies.

   YES  NO  Initials ____________

3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.

   YES  NO  Initials _______

I agree to take part in this study.

Assent by child/adolescent  Date

To the professional:
If the child does not sign the form but you believe the child has actively assented, please document on this form. State the specific behaviors (child shook head yes, child said “OK” after I described procedure, etc.).

________________________________________
________________________________________
________________________________________

Researcher  Date

IRB#: 0909-082  Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________ Please print (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________

Hospital Name: ____________________________________________________

The following information is requested:

- Hospital discharge summaries
- Pathologist’s reports on surgical specimens, bone marrow, CSF
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
- Treatment records (chemotherapy, radiation therapy, including chemo roadmaps)
- Consultations
- Pediatric Oncology CLINIC records
- Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
- Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.
E-mail: gretchen.williams@childrensmn.org

Telephone: 612 813 7115
Fax: 612 813 7108

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

____________________________________________    _____________________________
Printed Name of Parent or Guardian      Date Signed

____________________________________________    _____________________________
Signature of Parent or Guardian      Relationship to Patient

_______________________________________________________________________________________________________
Address             City       State          Zip Code

_____________________________________     _____________________________
Parent or Guardian Home Phone      Parent or Guardian Work Phone
Types I, II & III PPB HIPAA Authorization Form for Participation in The International PPB Treatment and Biology Registry

Health Insurance Portability and Accountability Act (HIPAA)
Authorization to Use/Disclose Protected Health Information for Research

International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects you and your child’s individually identifiable health information (protected health information). The privacy law requires you or your child to sign an authorization in order for researchers to be allowed to use or disclose your/your child’s protected health information for research purposes in the study entitled International PPB Treatment Study.

What protected health information may be used or disclosed?

Your/your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, tumor measurement, x-rays and scans, and pathology results
- Results of tests to monitor for side effects including hearing tests, heart tests, lung tests, learning ability
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

What will you or your child’s protected health information be used for?

The main reason to use your or your child’s health information is to be able to conduct research into PPB treatments and into scientific, biologic research on PPB. PPB is a very rare malignant disease in the lung of young children. It occurs in three forms: Types I, II, and III PPB. Because it is so rare, consistent treatment of a large group of children has never occurred, and treatment success is therefore very difficult to judge. In addition, PPB appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment Study has three purposes:

(1) For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease in the chest. This study collects information on treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

(2) For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink...
large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

(3) To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on PPB children and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store PPB tissue and to collect and store DNA from saliva or blood of PPB children and their mothers and their fathers.

In addition to these PPB research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

Who may disclose your/your child’s protected health information to the researchers?

If you agree to your child’s participation in this PPB study, the study researchers and their staff may obtain your or your child’s protected individual health information from the hospital and clinic where your child is treated.

With whom would the protected health information be shared?

Your/your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child’s hospital who not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital

What is the potential for re-disclosure of your/your child’s protected health information?

All reasonable efforts will be used to protect the confidentiality of your or your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your or your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your or your child’s confidentiality will be compromised.
What happens if I do not sign this permission form?

If you do not sign this permission form, your child will not be a part in this PPB research study for which your child is being considered.

For how long will you/your child’s protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

What are your or your child’s rights after signing this Authorization form?

You/your child have the right to withdraw from participating in this research. You have the right to revoke in writing your permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your permission to conduct the research and related activities such as oversight. Even if you revoke your permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If you wish to withdraw your permission, contact the investigator and you will be asked to complete a written form.

You have the right to choose not to sign this form. If you decide not to sign, your child will not participate in this PPB research. Refusing to sign will not affect the current or future care you/your child receives at your treatment institution and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you/your child choose to share private health information with anyone not directly related to this research, the federal law designed to protect your privacy may no longer protect the shared information.

What are you/your child’s rights to access your/your child’s protected health information?

Subject to certain legal limitations, you have the right to access your child’s protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. You may access this information only after the study analyses are complete. To request this information, you will need to contact your child's doctor or the Institutional Review Board at your child’s hospital. Findings from future research using material stored in the tissue bank established in this study (PPB tissue from your child and DNA from saliva or blood from your child and from the mother and the father) will not be available to you.

By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this PPB study to use and disclose your/your child’s protected health information for the purposes described above. You also permit you/your child’s doctors and other health care providers to disclose you/your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at your child’s hospital.
CERTIFICATIONS AND SIGNATURE SECTION

I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed.

Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject) OR Research Subject’s Authorized Representative (such as Parent or Guardian) Date

Printed name of Research Subject’s Authorized Representative Representative’s relationship to Research Subject (for example: “mother” or “father” or “guardian”)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):

IRB#: 0909-082 Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
TAKING PART IN GENETIC RESEARCH: ISSUES TO CONSIDER

You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

Considering Possible Benefits
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

Considering Possible Risks
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child's point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

Insurance Coverage
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

Employment or Other Qualification Decisions
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

Emotional Effects of Genetic Information
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
• what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
• if the researcher will keep other information with the sample
• if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
• What is the purpose of the study?
• What is my doctor's involvement in the study?
• Who is paying for the study?
• Will I be able to get the information from the genetic testing?
• Will anyone else get the information from the genetic testing?
• Will the information from the study help me or my child?
• Will the information from the study help other people with this disease or condition?
• How are the costs of the study being paid, and will my insurance company be billed?
• Will the information be in my or my child's medical record?
• What will happen to the sample after the study is done, and do I have any control of that?
• Will any other information be kept with the sample?
• Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child's physician if you have questions or concerns. You may also contact Children's Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child's care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer's. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your gender
Your racial or ethnic group
Your age
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
How is my privacy protected?
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

What are the risks to me if I give my tissue to research?
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

Can I change my mind?
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

What if I have more questions?
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
International Pleuropulmonary Blastoma Treatment and Biology Registry

NOTICE OF PRIVACY PRACTICES

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry's legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to "you" or "your" in this Notice, we refer to the patient. When we refer to types of disclosures of information to "you," we mean disclosures to the patient, the patient’s guardian, or the person legally authorized to receive information about the patient.

YOUR PRIVACY RIGHTS

Confidential communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke your written permission (authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment and Biology Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

This Treatment and Biology Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

OTHER USES AND DISCLOSURES

Research: This study collects family medical history and establishes a collection of specimens from PPB patients and their parents for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain
files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small. In some cases, where there is only a minimal risk to your privacy (for example, a research project comparing the treatment and outcome of all patients who received chemotherapy for PPB) we may disclose information about you without your written authorization. We will only disclose information about you for research without your authorization when the approval process determines that there is only a minimal risk to your privacy, and we have initiated steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Correspondence: If you have indicated on the consent form that yes, you will allow the PPB Treatment and Biology Registry to contact you with information about new studies or other Registry services that may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this contact could be by leaving messages on a home answering machine or voice mail, by email or by the Postal Service.

Other uses and disclosures: Disclosures of health information not covered by this Notice or the laws that apply to PPB Treatment and Biology Registry will be made only with your written permission.

FOR MORE INFORMATION
If you want more information about your privacy rights, are concerned that the PPB Treatment and Biology Registry has violated your privacy rights, or you disagree with a decision that we made about access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2525 Chicago Avenue South
Minneapolis, MN 55404
(612) 813-7115
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children’s and you will not be retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights
U.S. Department of Health and Human Services
233 North Michigan Avenue, Suite 240
Chicago, IL 60601
(312) 886-2359 or 1-800-368-1019
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes will apply to information we already have about you and information we receive about you in the future. We will provide an updated Notice to you when you request one. We will also post the most current Notice in public areas and on the PPB Treatment and Biology Registry Children’s Web site at www.ppbregistry.org

The effective date of this Notice is May 8, 2009.
Appendix IV – B: Non-Children's Hospitals and Clinics of Minnesota Institutions: Type Types II and III PPB - Consenting Documents
INTRODUCTION

You are being asked to participate in a childhood cancer research study called a Treatment and Biology Registry; it is for children with the rare childhood lung tumor called pleuropulmonary blastoma (PPB). A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue and saliva or blood) from patients with PPB and from their parents. To participate, your agreement is necessary, but it is your choice. You are being asked to participate because your child has been diagnosed with Type II or Type III PPB.

- If you are a parent or legal guardian of a child who may be included in this research study, your permission is required for your child to be included.

- If you are the PPB patient and are old enough to consent to treatment without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.

- Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (generally, children ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

Part 1: Collecting data on children with Types II and III PPB and on their treatment. Children diagnosed with Types II or III PPB will be treated according to decisions at their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

Part 2: The second part of this study involves research into the biology of PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens of the tumor and saliva and/or blood specimens for biological research.

Your doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your health care team. If you have any questions, you can ask your doctor or members of the Registry staff for more explanation.
This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from many countries. The research is coordinated by The International PPB Registry based at Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and Children's Hospitals of Washington University, St Louis, Missouri USA; and Children’s National Medical Center, Washington, D. C., USA.

WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?
You are being asked to take part in this study because your child has a rare malignant (cancerous) tumor called pleuropulmonary blastoma (PPB).

1. **What is PPB and What are Types II and III PPB?**: PPB is a very rare tumor. It arises in tissue called “pleura” (pleura covers the inside of the chest cavity and also covers the surface of the lung); PPB can also arise in the “pulmonary” tissue, which is the lung itself. PPB is usually a cancer of young children, under age 72 months, but it may occur in older children. PPB is not related to the lung cancers which occur in adults.

   There are three forms of PPB called Types I, II, and III PPB. Types II and III PPB are quite serious forms of childhood cancer. Types II and III PPB can spread to other parts of the body and special x-ray tests (imaging studies) are used to evaluate this.

2. **Treatment of Types II and III PPB**: Children with Types II and III PPB require surgery, chemotherapy and perhaps radiation therapy for treatment. It is not known what chemotherapy drugs and schedule of drugs are the best for Types II and III PPB. The reason for this is that PPB is very rare. No large group of children with Types II or III PPB has ever been collected together to determine what treatments work best.

   This research study suggests surgery as complete as possible for Types II and III PPB. Sometimes surgery to remove the tumor is not done until chemotherapy has been used to shrink the tumor. Your child’s doctor will decide what chemotherapy drugs and schedule to recommend for treatment of your child. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

   This Registry will collect information about how children with Types II and III PPB cases are treated. After enough cases have been collected and enough time has passed to learn how the children have done, the results will be made available to help doctors learn what therapies may be helpful for Types II and III PPB.

3. **PPB Biology and Genetics**: In 30-40% of cases, children with PPB or their family members have other medical conditions. One of these conditions is lung cysts which may develop into serious cancers. The evolution of lung cysts into serious solid tumors and the familial predisposition to certain illnesses is called the “biology of PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes some family members to PPB or other conditions and may be passed from generation to generation. A mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB cases have this mutation and how it may cause the disease.

   The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare...
conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.

WHAT DOES THE TREATMENT AND BIOLOGY REGISTRY INVOLVE?

Study Part 1: Collection of Data on Treatment of Types II and III PPB:

There are three major ways to treat cancer and PPB:

- **Surgery** to remove cancer tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells.
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells.

Types II and III PPB tumors often affect large areas of the lung and chest cavity; these PPBs cannot be removed totally by surgery. Standard (usual) treatment around the world for children with Types II and III PPB is surgery and chemotherapy, and sometimes radiation therapy. Instead of major surgery, large tumors are sometimes sampled (biopsied) first; then chemotherapy is used to shrink the tumor; then surgery is used to try to remove remaining tumor. For chemotherapy, there are many different anti-cancer drugs and many possible combinations of these drugs. Around the world, there is no standard combination or standard schedule of anti-cancer drugs for treatment of Types II and III PPB.

Children in this study will have surgery to try to remove the PPB (or a biopsy for diagnosis first with surgery later). Then your child’s doctor and his or her colleagues will decide what chemotherapy drugs and schedule to use. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose. Your child’s doctors will also decide how much surgery should be recommended to remove the PPB tumor and whether radiation therapy should be used.

This research will collect information on how children with Types II and III PPB are treated and what is their outcome.

Study Part 2: Research into PPB Biology and Genetics:

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB. This study asks for permission to collect family medical history information, to store excess portions of the child’s Type II or III PPB tumor, and to collect and store saliva or blood from the child, from the mother and from the father for research uses.

WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?

Study Part 1: Types II and III PPB are very rare and there is no established “standard” or “best” therapy. Around the world, children with PPB have been treated according to decisions made case-by-case over many years in many different hospitals by many different physicians. No treatment has been tested in a large group of Types II and III PPB patients. The goal of this research study is to collect treatment information for Type II and III PPB children and to try to learn how well certain treatments work. Future treatments can be compared to this treatment in order to measure improvements.

Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from PPB patients and their parents for research to try to answer some of these questions.

In summary, the goals of this Treatment and Biology Registry are:
1) To collect data on treatment of children with Types II and III PPB and to learn the success rates of different treatments.

2) To collect family medical histories and to collect and save Types II and III PPB tumor samples and saliva or blood samples from the PPB child and from the mother and father in order to learn more about the biology of PPB and genetic factors in PPB.

HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
We estimate that about 20-40 Type II or III PPB patients per year will be collected in this Registry.

WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?
Study Part 1. Treatment of Types II and III PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: how much surgery and what chemotherapy medications and schedule to use, and whether to recommend radiation therapy. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

This research will collect information about your child and on how the Type II or III PPB was treated. This project also involves collecting x-rays and tissue from surgery to review and confirm the diagnosis of Type II or III PPB.

Study Part 2. Biology and Genetics of PPB: The biology and genetic studies of this research involve the following biological samples:

- From the child with PPB:
  - After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies.
  - Collecting blood or saliva for DNA samples for research studies.

- From the Mother:
  - Collecting blood or saliva for DNA samples for research studies.

- From the Father:
  - Collecting blood or saliva for DNA samples for research studies.

In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.

HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?
Your child will be followed indefinitely in order to determine the outcome of the Type II or III PPB.

PPB tumor tissue from the time of initial or subsequent biopsy or surgery will be saved indefinitely to be used for research into causes and treatment of PPB. Blood or saliva samples from your child and from the mother and father will also be saved indefinitely for research into causes, biology, and treatment of PPB.
CAN MY CHILD STOP BEING IN THIS STUDY?
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)

WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child’s medical data in the Registry will help physicians and researchers learn more about PPB and its treatment. The information may be helpful in the treatment of PPB in the future. Also, study of biologic specimens in this Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat PPB more successfully.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of Types II and III PPB patients for evaluation of the results of their treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or hospital.

HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?
When a childhood cancer research study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with PPB are to be treated (your child’s doctor and his or her colleagues make those decisions), so it is not mandatory that this Registry has been reviewed and approved at your child’s hospital. Even though it may not be mandatory, some hospitals do choose to formally review a project like this.

This PPB Treatment and Biology Registry project has been approved at the children’s hospitals in Minnesota, Missouri, and Washington, D.C. who are coordinating the research.
Regardless of whether your child’s doctor and hospital have specifically approved this research project, your consent to participate is required. Many institutions encourage parents to consider participation in Registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

**WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?**

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.

The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.

**WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**

There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

**WHAT ARE MY RIGHTS IF I TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?**

Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at your local hospital will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.

**WHO CAN ANSWER MY QUESTIONS ABOUT THIS REGISTRY?**

You can talk to your local doctor about any questions or concerns you have about this research. Your physician may direct you to a local Research or Ethics Board administrator at your hospital who can also help you. You may also choose to discuss participation with support personnel at your child’s hospital, such as social workers or family support counselors.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org). You may also call the Institutional Review Board Administrator at Children’s Hospitals and Clinics of Minnesota at (621) 813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES
You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

Part 1: Collection of Information on Type II and III PPB Treatment

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I agree to have my child be a part of the Treatment and Biology Registry Part 1: Collection of Information on Types II and III PPB Treatment.

PATIENT’S NAME ____________________________________________

Printed

Parent/legal guardian ____________________________________________

Print name ______________ Signature ______________

Relationship to patient: ___________________________ DATE ___________________________

Please also answer this question:
Researchers studying PPB would like your permission to be able to contact you in the future if new PPB research topics are identified for which your participation would be helpful.

Do you agree to be contacted in the future about additional, special PPB research studies?

YOU DO NOT NEED TO AGREE TO THIS.

_____ I agree to be contacted in the future _____ I do not agree to be contacted in the future

IF YOU AGREE:

Name: ______________________________

Address: ______________________________

City, State, Postal/Zip Code: ______________________________

Telephone Number: ______________________________

Email address: ______________________________

IRB#: 0909-082
Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB and possible genetic factors which may be responsible for some cases of PPB. These research activities are separate from collecting data on how Types II and III PPB are treated.

We ask that the PPB patient and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the collection of Types II and III PPB Treatment, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in these studies without taking part in Part 1 on Types II and III PPB Treatment.)

WHAT DOES THIS PPB BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:

1. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.
2. To save leftover PPB tumor tissue (if available) from your child’s biopsy and/or surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies.
3. To collect and save saliva or blood samples from your child and from each biological parent for research.

The amount of saliva collected will be about 2 tablespoons (30 ml) and the amount of blood will be about 2 teaspoons (10 ml). In most cases, saliva will be collected. PPB tumor tissue will be taken from the tumor removed at surgery after all diagnostic requirements are satisfied.

Specimens saved in this Biology Registry will be used to learn many details about PPB cancer cells and any normal cells that might surround the cancer cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how the cancer is different from normal tissue. DNA from saliva or blood or tumor tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s tumor tissue and your child’s and your saliva or blood specimens will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for research into familial patterns of PPB and related
diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this Treatment and Biology Registry.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

**HOW LONG WILL SPECIMENS BE SAVED FOR BIOLOGY RESEARCH?**
Tumor tissue, saliva or blood specimens, and family medical histories will be saved indefinitely.

**CAN MY CHILD OR I STOP BEING PART OF THIS BIOLOGY REGISTRY?**
Yes. You can inform the Treatment and Biology Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

**ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS BIOLOGY RESEARCH?**
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB. It is possible that your child’s doctor or hospital is doing some biology research on tumors and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

**ARE THERE ANY BENEFITS?**
There is no direct benefit to you or your child from participating in the PPB Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.

**ARE THERE ANY RISKS?**
The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private.
Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.

WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?
If you have any questions, please talk to your doctor or other patient support personnel at your child’s hospital.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org). You may also call the Institutional Review Board Administrator at Children’s Hospitals and Clinics of Minnesota at (612) 813-7646 in Minneapolis, Minnesota USA.

A document called "How is Tissue Used for Research?" is attached to this consent form.
MAKING YOUR CHOICE ABOUT PARTICIPATING IN PPB BIOLOGY REGISTRY

One parent can authorize participation of a child in Part 2: the PPB Biology Research Registry. For the parents to take part, the patient’s mother must authorize her own participation and the patient’s father must authorize his own participation. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s PPB care.

After reading each sentence, circle "Yes" or "No" and write your signature and date in the spaces provided.

Consent for Participation in PPB Biology Registry Research:
Family Medical History and Saving Tumor Tissue and Saliva or Blood for Research

1. Your Child’s Participation in PPB Biology Registry
I agree to allow my child’s family medical history to be collected. I also agree to allow saliva or blood samples from my child to be collected and saved and to allow any leftover PPB tumor tissue (if available) from my child to be saved for research studies related to PPB.

Yes  No  _________________________  __________________
Signature of parent/guardian              relationship to patient

____________________
Date

2. PPB Patient’s MOTHER’S Participation in PPB Biology Registry
I agree to allow my family medical history to be collected. I also agree to allow my saliva or blood samples to be collected and saved for research studies related to PPB.

Yes  No   ____________________________    _____________________
Signature of MOTHER          Date

3. PPB Patient’s FATHER’S Participation in PPB Biology Registry
I agree to allow my family medical history to be collected. I also agree to allow my saliva or blood samples to be collected and saved for research studies related to PPB.

Yes  No   ____________________________   _____________________
Signature of FATHER            Date

IRB#: 0909-082
Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
Types II & III PPB Informed Assent
for Participation in The International PPB Treatment and Biology Registry

Name: ____________________________

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Registry Office:
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN  55404   USA

Assent Form for Child or Adolescent Ages 7-17 with Type II or Type III PPB

We are asking you to take part in a research study because you have pleuropulmonary blastoma (PPB). PPB is a rare type of cancer in the lung. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about PPB and how to treat it. We will do this by collecting records on how doctors treat children with Types II & III PPB. Based on past experiences, the Registry makes suggestions on how PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want your permission as well. Children and teens with Types II and III PPB will be treated with surgery and chemotherapy. Some may also need to receive radiation therapy. Chemotherapy is a type of strong medicine that destroys cancer cells. Radiation therapy uses strong x-rays to destroy cancer cells. Chemotherapy and radiation therapy can also cause side effects that could make you temporarily feel sicker.

As part of this study, information about your illness and how you respond to treatment is sent to the main PPB Study research office. Doctors from around the world want to share information about treating children and teenagers who have PPB. By sharing information, we can more quickly learn the best ways to treat cancer. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also receive a sample of the tumor that was removed from your chest so that they can learn in the future about how and perhaps why PPB cancers exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it. We will also ask for a sample of saliva, and maybe a small tube of blood, from you to store for future research into why some people have PPB.

Your mother or father or guardian can help you decide whether to agree to this scientific study. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.
<table>
<thead>
<tr>
<th>Question</th>
<th>Option 1</th>
<th>Option 2</th>
<th>Initials</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My tissue and saliva or blood may be sent to the PPB Study office to be used in research about PPB.</td>
<td>YES</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>2. My leftover tissue, blood, or saliva may be kept by the PPB Study office for use in future research studies.</td>
<td>YES</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.</td>
<td>YES</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>

I agree to take part in this study.

Assent by child/adolescent ______________________________ Date __________________________

To the professional:
If the child does not sign the form but you believe the child has actively assented, please document on this form. State the specific behaviors (child shook head yes, child said “OK” after I described procedure, etc.).

Researcher ______________________________ Date __________________________

IRB#: 0909-082
Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________

Please print (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________

Hospital Name: ____________________________________________________

The following information is requested:

- Hospital discharge summaries
- Pathologist’s reports on surgical specimens, bone marrow, CSF
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
- Treatment records (chemotherapy, radiation therapy, including chemo roadmaps)
- Consultations
- Pediatric Oncology CLINIC records
- Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
- Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.
E-mail: gretchen.williams@childrensmn.org

Telephone: 612 813 7115
Fax: 612 813 7108

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

Printed Name of Parent or Guardian: _____________________________ Date Signed: _____________________________

Signature of Parent or Guardian: _____________________________ Relationship to Patient: _____________________________

Address: ____________________________________________ City: _____________________________ State: __________ Zip Code: _____________________________

Parent or Guardian Home Phone: _____________________________ Parent or Guardian Work Phone: _____________________________
The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects you and your child’s individually identifiable health information (protected health information). The privacy law requires you or your child to sign an authorization in order for researchers to be allowed to use or disclose your/your child’s protected health information for research purposes in the study entitled International PPB Treatment Study.

What protected health information may be used or disclosed?

Your/your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, tumor measurement, x-rays and scans, and pathology results
- Results of tests to monitor for side effects including hearing tests, heart tests, lung tests, learning ability
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

What will your or your child’s protected health information be used for?

The main reason to use your or your child’s health information is to be able to conduct research into PPB treatments and into scientific, biologic research on PPB. PPB is a very rare malignant disease in the lung of young children. It occurs in three forms: Types I, II, and III PPB. Because it is so rare, consistent treatment of a large group of children has never occurred, and treatment success is therefore very difficult to judge. In addition, PPB appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment Study has three purposes:

1. For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease in the chest. This study collects information on treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

2. For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed
necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

3. To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on PPB children and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store PPB tissue and to collect and store DNA from saliva or blood of PPB children and their mothers and their fathers.

In addition to these PPB research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

Who may disclose your/your child’s protected health information to the researchers?

If you agree to your child’s participation in this PPB study, the study researchers and their staff may obtain your or your child’s protected individual health information from the hospital and clinic where your child is treated.

With whom would the protected health information be shared?

Your/your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child’s hospital who not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital

What is the potential for re-disclosure of your/your child’s protected health information?

All reasonable efforts will be used to protect the confidentiality of your or your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your or your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your or your child’s confidentiality will be compromised.
What happens if I do not sign this permission form?

If you do not sign this permission form, your child will not be a part in this PPB research study for which your child is being considered.

For how long will you/your child’s protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

What are your or your child’s rights after signing this Authorization form?

You/your child have the right to withdraw from participating in this research. You have the right to revoke in writing your permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your permission to conduct the research and related activities such as oversight. Even if you revoke your permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If you wish to withdraw your permission, contact the investigator and you will be asked to complete a written form.

You have the right to choose not to sign this form. If you decide not to sign, your child will not participate in this PPB research. Refusing to sign will not affect the current or future care you/your child receives at your treatment institution and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you/your child choose to share private health information with anyone not directly related to this research, the federal law designed to protect your privacy may no longer protect the shared information.

What are you/your child’s rights to access your/your child’s protected health information?

Subject to certain legal limitations, you have the right to access your child’s protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. You may access this information only after the study analyses are complete. To request this information, you will need to contact your child's doctor or the Institutional Review Board at your child’s hospital. Findings from future research using material stored in the tissue bank established in this study (PPB tissue from your child and DNA from saliva or blood from your child and from the mother and the father) will not be available to you.

By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this PPB study to use and disclose your/your child’s protected health information for the purposes described above. You also permit you/your child’s doctors and other health care providers to disclose your/your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at your child’s hospital.
CERTIFICATIONS AND SIGNATURE SECTION

I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed.

Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject) OR Research Subject’s Authorized Representative (such as Parent or Guardian) Date

Printed name of Research Subject’s Authorized Representative Representative’s relationship to Research Subject (for example: “mother” or “father” or “guardian”)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):

IRB#: 0909-082 Initial IRB Approval: 12/22/2009
Most recent IRB approval: 07/22/2015
TAKING PART IN GENETIC RESEARCH: ISSUES TO CONSIDER

You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

Considering Possible Benefits
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

Considering Possible Risks
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child's point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

Insurance Coverage
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

Employment or Other Qualification Decisions
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

Emotional Effects of Genetic Information
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
• what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
• if the researcher will keep other information with the sample
• if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
• What is the purpose of the study?
• What is my doctor's involvement in the study?
• Who is paying for the study?
• Will I be able to get the information from the genetic testing?
• Will anyone else get the information from the genetic testing?
• Will the information from the study help me or my child?
• Will the information from the study help other people with this disease or condition?
• How are the costs of the study being paid, and will my insurance company be billed?
• Will the information be in my or my child’s medical record?
• What will happen to the sample after the study is done, and do I have any control of that?
• Will any other information be kept with the sample?
• Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child’s physician if you have questions or concerns. You may also contact Children’s Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child’s care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
HOW IS TISSUE USED FOR RESEARCH? WHAT YOU NEED TO KNOW

You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer's. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your gender
Your racial or ethnic group
Your age
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
Treatment you have received
Your family history
Your medical history.

How is my privacy protected?
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

What are the risks to me if I give my tissue to research?
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

Can I change my mind?
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

What if I have more questions?
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
NOTICE OF PRIVACY PRACTICES

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry’s legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to “you” or “your” in this Notice, we refer to the patient. When we refer to types of disclosures of information to “you,” we mean disclosures to the patient, the patient’s guardian, or the person legally authorized to receive information about the patient.

YOUR PRIVACY RIGHTS

Confidential communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke your written permission (authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment and Biology Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

This Treatment and Biology Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

OTHER USES AND DISCLOSURES

Research: This study collects family medical history and establishes a collection of specimens from PPB patients and their parents for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain...
files and data in locked offices and on password-protected computers. Patient names will be replaced in
the files and the computer records with randomly-assigned Registry case numbers. If information from
this Registry is published or presented at scientific meetings, your child’s name and other personal
information will not be used. We cannot guarantee total privacy, but the chance that personal information
will be given to someone else is very small. In some cases, where there is only a minimal risk to your
privacy (for example, a research project comparing the treatment and outcome of all patients who
received chemotherapy for PPB) we may disclose information about you without your written
authorization. We will only disclose information about you for research without your authorization when
the approval process determines that there is only a minimal risk to your privacy, and we have initiated
steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your
child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health
records. In the future, people who do research on these specimens may need to know more about your
health. While this Registry may give them certain details about your child’s or your health, it will not give
them your name, address, phone number, or any other information that will let the researchers know who
you are.

Correspondence: If you have indicated on the consent form that yes, you will allow the PPB Treatment
and Biology Registry to contact you with information about new studies or other Registry services that
may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this
contact could be by leaving messages on a home answering machine or voice mail, by email or by the
Postal Service.

Other uses and disclosures: Disclosures of health information not covered by this Notice or the laws
that apply to PPB Treatment and Biology Registry will be made only with your written permission.

FOR MORE INFORMATION
If you want more information about your privacy rights, are concerned that the PPB Treatment and
Biology Registry has violated your privacy rights, or you disagree with a decision that we made about
access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2525 Chicago Avenue South
Minneapolis, MN 55404
(612) 813-7115
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children’s and you will not be
retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights
U.S. Department of Health and Human Services
233 North Michigan Avenue, Suite 240
Chicago, IL 60601
(312) 886-2359 or 1-800-368-1019
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes
will apply to information we already have about you and information we receive about you in the future.
We will provide an updated Notice to you when you request one. We will also post the most current
Notice in public areas and on the PPB Treatment and Biology Registry Children’s Web site at
www.ppbregistry.org

The effective date of this Notice is May 8, 2009.
Appendix IV – C: Type I PPB – Sample Consenting Documents
Type I PPB - Sample Informed Consent

International PPB Treatment and Biology Registry

Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry

PPB Treatment and Biology Registry Office
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN 55404 USA

RESEARCH CONSENT FORM – Type I PPB

INTRODUCTION
You are being asked to participate in a childhood cancer research study called a Treatment and Biology Registry; it is for children with the rare childhood lung tumor called pleuropulmonary blastoma (PPB). A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue) from patients with PPB. To participate, your agreement is necessary, but it is your choice. You are being asked to participate because your child has been diagnosed with Type I PPB.

- If you are a parent or legal guardian of a child who may be included in this Treatment and Biology Registry, your permission is required for your child to be included.

- If you are a Type I PPB patient and are old enough to consent to treatment without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.

- Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (usually ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

Part 1: Collecting data on children with Type I PPB (“cystic PPB”) and on their treatment. Children diagnosed with Type I PPB will be treated according to decisions at their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

Part 2: The second part of this study involves research into the biology of PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens of the lung cyst (cystic tumor) for biological research.

Your doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your
health care team. If you have any questions, you can ask your doctor or members of the Registry staff for more explanation.

This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from many countries. The research is coordinated by The International PPB Registry based at Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and Children's Hospitals of Washington University, St Louis, Missouri USA; and Children’s National Medical Center, Washington, D. C., USA.

WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?
You are being asked to take part in this study because your child has a rare malignant (cancerous) tumor called Type I pleuropulmonary blastoma (Type I PPB, also called cystic PPB).

1. **What is PPB and Type I PPB?** PPB is a very rare tumor. It arises in tissue called “pleura” (pleura covers the inside of the chest cavity and also covers the surface of the lung); PPB can also arise in the “pulmonary” tissue, which is the lung itself. PPB is usually a cancer of young children, under age 72 months, but it may occur in older children. PPB is not related to the lung cancers which occur in adults.

There are three types of PPB: Types I, II, and III PPB. Type I PPB is a cyst in the chest. On x-rays, the cysts of Type I PPB look like benign (non-cancerous) lung cysts of young children called “CCAM” or “CPAM”, which your doctor can explain to you. Type I PPB is diagnosed under the microscope after a cyst is surgically removed. Type I PPB is malignant; it is an early malignancy which is usually cured. If Type I PPB is not cured while it is Type I, it can progress to the much more serious forms of PPB called Type II and Type III PPB. There are no known instances of Type I PPB spreading to other parts of the body.

2. **Treatment of Type I PPB:** Children with Type I PPB require surgery to remove the lung cyst as completely as possible. After surgery, there are different opinions about whether more treatment (chemotherapy; anti-cancer drug therapy) is useful to cure children. Some pediatric cancer doctors choose to use chemotherapy for Type I PPB; some choose not to use it. The reason doctors do not “know” what is best for Type I PPB is that it is so rare. No large group of children with Type I PPB has ever been collected together to determine what treatments work best.

This research study suggests surgery as complete as possible for Type I PPB. Then your child’s doctor will decide whether to recommend chemotherapy. If your child’s doctor does recommend chemotherapy, he or she may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

This Registry will collect information about how Type I PPB cases are treated. After enough cases have been collected and enough time has passed to learn how the children have done, the results will be made available to help doctors learn what therapies may be helpful for Type I PPB.

3. **PPB Biology and Genetics:** In 30-40% of cases, children with PPB or their family members have other medical conditions. One of these conditions is lung cysts which may develop into serious cancers. The evolution of lung cysts into serious solid tumors and to certain illnesses is called the “biology of PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes some family members to PPB or other conditions and may be passed from generation to generation. A mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB cases have this mutation and how it may cause the disease.
The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.

WHAT DOES THE TREATMENT AND BIOLOGY REGISTRY INVOLVE?

**Study Part 1: Collection of Data on Treatment of Type I PPB:**
There are three major ways to treat cancer and PPB:

- **Surgery** to remove cancer tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells.
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells.

Surgery is necessary for Type I PPB. It is not known whether chemotherapy for Type I PPB improves the chance for cure; some doctors recommend chemotherapy; other doctors do not. Your doctor and his or her colleagues will decide whether to recommend chemotherapy for your child. Radiation therapy is not used for Type I PPB.

This research will collect information on how children with Type I PPB are treated and what is their outcome.

**Study Part 2: Research into PPB Biology and Genetics:**

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB. This study asks for permission to collect family medical history information and to store excess portions of the child’s Type I PPB tumor (cyst) for research uses.

WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?

**Study Part 1: Type I PPB is very rare and there is no established “standard” or “best” therapy. Surgery is necessary. After that, there is not enough information to know whether chemotherapy cures more children than surgery alone would do. The goal of this research study is to collect information on how Type I PPB is treated and analyze the information to see whether the use of chemotherapy after surgery helps cure more children.**

**Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.**

In summary, the goals of this Treatment and Biology Registry are:

1) To collect data on treatment of Type I PPB and to learn the success rates of different treatments.

2) To collect family medical histories and to collect and save Type I PPB cyst samples from the PPB child to learn more about the biology of PPB and genetic factors in PPB.

HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?

We estimate that about 20-30 Type I PPB patients per year from around the world will be collected in this Registry.
WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?
Study Part 1. Treatment of Type I PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: how much surgery and whether to use chemotherapy. This research will collect information about your child and on how the Type I PPB was treated. This also involves collecting x-rays and tissue from surgery to review and confirm the diagnosis of Type I PPB.

Study Part 2. Biology and Genetics of PPB: The biology and genetic studies of this research involve the following biological samples:
- From the child with PPB:

After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies. In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.

HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?
Your child will be followed indefinitely in order to determine the outcome of the Type I PPB.

PPB cyst tissue from the time of initial surgery will be saved indefinitely to be used for research into causes and treatment of PPB.

CAN MY CHILD STOP BEING IN THIS TREATMENT AND BIOLOGY REGISTRY?
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)

WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child's medical data in the Registry will help physicians and researchers learn more about PPB and its treatment. The information may be helpful in the treatment of PPB in the future. Also, study of biologic specimens in this Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat PPB more successfully.
WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?

You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of Type I PPB patients for evaluation of the results of their treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or hospital.

HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?

When a childhood cancer research study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with PPB are to be treated (your child’s doctor and his or her colleagues make those decisions), so it is not mandatory that this Registry has been reviewed and approved at your child’s hospital. Even though it may not be mandatory, some hospitals do choose to formally review a project like this.

This PPB Treatment and Biology Registry project has been approved at the children’s hospitals in Minnesota, Missouri, and Washington, D.C. who are coordinating the research.

Regardless of whether your child’s doctor and hospital have specifically approved this research project, your consent to participate is required. Many institutions encourage parents to consider participation in Registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.

The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.

WHAT ARE THE COSTS OF TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?

There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at your local hospital will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.
WHO CAN ANSWER MY QUESTIONS ABOUT THIS REGISTRY?

You can talk to your local doctor about any questions or concerns you have about this research. Contact your doctor __________________ [name(s)] at __________________ [telephone number]. Your physician may direct you to a local Research or Ethics Board administrator at your hospital who can also help you. You may also choose to discuss participation with support personnel at your child’s hospital, such as social workers or family support counselors.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org) You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (612) 813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES

You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

**Part 1: Collection of Information on Type I PPB Treatment**

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I agree to have my child be a part of the Treatment and Biology Registry Part 1: Collection of Information on Type I PPB Treatment.

PATIENT’S NAME ________________________________

Printed

Parent/legal guardian _______________________ ___________________________

Print name Signature

Relationship to patient: __________________ DATE _____________________

Please also answer this question:

Researchers studying PPB would like your permission to be able to contact you in the future if new PPB research topics are identified for which your participation would be helpful.

Do you agree to be contacted in the future about additional, special PPB research studies? (You do not need to agree to this.)

_____ I agree to be contacted in the future _____ I do not agree to be contacted in the future

IF YOU AGREE:

Name: ________________________________

Address: ________________________________

________________________________________

City, State, Postal/Zip Code: ________________________________

Telephone Number: ________________________________

Email address: ________________________________
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB and possible genetic factors which may be responsible for some cases of PPB. These research activities are separate from collecting data on how Type I PPB is treated.

We ask that the PPB patient and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the collection of Type I PPB Treatment, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in biology studies without taking part in Part 1 on Type I PPB Treatment.)

WHAT DOES THIS PPB BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:

4. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.

5. To save leftover PPB cyst tissue (if available) from your child’s surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies. Specimens saved in this Biology Registry will be used to learn many details about PPB cancer cells and any normal cells that might surround the cancer cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how the cancer is different from normal tissue. DNA from tumor tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s cyst tissue will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for research into familial patterns of PPB and related diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this Treatment and Biology Registry. Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.
Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

**HOW LONG WILL SPECIMENS BE SAVED FOR BIOLOGY RESEARCH?**
Tumor tissue and family medical histories will be saved indefinitely.

**CAN MY CHILD OR I STOP BEING PART OF THIS BIOLOGY REGISTRY?**
Yes. You can inform the Treatment and Biology Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

**ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS BIOLOGY RESEARCH?**
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB. It is possible that your child’s doctor or hospital is doing some biology research on tumors and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

**ARE THERE ANY BENEFITS?**
There is no direct benefit to you or your child from participating in the PPB Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.

**ARE THERE ANY RISKS?**
The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private. Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.

**WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?**
If you have any questions, please talk to your doctor or other patient support personnel at your child’s hospital.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensminn.org). You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (612) 813-7646 in Minneapolis, Minnesota USA.
A document called "How is Tissue Used for Research?" is attached to this consent form.

MAKING YOUR CHOICE ABOUT PARTICIPATING IN PPB BIOLOGY REGISTRY
One parent can authorize participation of a child in Part 2: the PPB Biology Research Registry. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s PPB care.

After reading each sentence, circle "Yes" or "No" and write your signature and date in the spaces provided.

Consent for Participation in PPB Biology Registry Research:
Family Medical History and Saving Cyst Tissue for Research

1. Your Child’s Participation in PPB Biology Registry
I agree to allow my child’s family medical history to be collected. I also agree to allow any leftover PPB cyst tissue (if available) from my child to be saved for research studies related to PPB.

Yes  No  _________________________  __________________
Signature of parent/guardian  relationship to patient

____________________
Date

__________________________________________  Date
Physician/Researcher obtaining consent
Type I PPB Sample Informed Assent for Participation in The
International PPB Treatment and Biology Registry

Name: ____________________________

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY
REGISTRY

Study Office:
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN  55404   USA

Assent Form for Child or Adolescent Ages 7-17 with Type I PPB

We are asking you to take part in a research study because you have pleuropulmonary blastoma (PPB). PPB is a rare type of cancer in the lung. A research study is when doctors work together to try out new ways to help people who are sick. This study wants to learn more about PPB and how to treat it. We will do this by collecting records on how doctors treat children with Type I PPB. Based on past experiences, the Registry makes suggestions on how PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want to include you as well. Children and teens with Type I PPB who are part of this study may be treated with surgery and chemotherapy. Your doctor will decide whether to recommend this to your parents and will discuss it with them and you. Chemotherapy is a type of strong medicine that destroys cancer cells. Chemotherapy can also cause side effects that could make you temporarily feel sicker.

As part of a study, information about your illness and your surgery and other possible treatments is sent to the main PPB Study research office. Doctors from around the world want to share information about treating children and teenagers who have Type I PPB. By sharing information, we can more quickly learn the best ways to treat cancer. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also send receive a sample of the cyst that was removed from your chest so that they can learn in the future about how and perhaps why PPB cancers exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it.

Your mother or father or guardian can help you decide whether to agree to this scientific study. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.
Please answer the following questions by circling either YES or NO and entering your initials.

1. My tissue may be sent to the PPB Study office to be used in research about PPB.
   
   YES  NO  Initials _______

2. My leftover tissue may be kept by the PPB Study office for use in future research studies.
   
   YES  NO  Initials _______

3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.
   
   YES  NO  Initials _______

I agree to take part in this study.

Assent by child/adolescent  
Date

To the professional:
If the child does not sign the form but you believe the child has actively assented, please document on this form. State the specific behaviors (child shook head yes, child said “OK” after I described procedure, etc.).

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Physician/Researcher obtaining consent  
Date

IRB#  
Initial IRB Approval:
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________

Please print (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________

Hospital Name: ____________________________________________________

The following information is requested:

- Hospital discharge summaries
- Pathologist’s reports on surgical specimens, bone marrow, CSF
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
- Treatment records (chemotherapy, radiation therapy, including chemo roadmaps)
- Consultations
- Pediatric Oncology CLINIC records
- Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
- Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.
E-mail: gretchen.williams@childrensmn.org

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

____________________________________________    _____________________________
Printed Name of Parent or Guardian      Date Signed

____________________________________________    _____________________________
Signature of Parent or Guardian      Relationship to Patient

_______________________________________________________________________________________________________
Address             City       State          Zip Code

_____________________________________     _____________________________
Parent or Guardian Home Phone      Parent or Guardian Work Phone
Types I, II & III PPB Sample HIPAA Authorization Form for Participation in The International PPB Treatment and Biology Registry

Health Insurance Portability and Accountability Act (HIPAA)
Authorization to Use/Disclose Protected Health Information for Research

International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects you and your child’s individually identifiable health information (protected health information). The privacy law requires you or your child to sign an authorization in order for researchers to be allowed to use or disclose your/your child’s protected health information for research purposes in the study entitled International PPB Treatment Study.

What protected health information may be used or disclosed?

Your/your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, tumor measurement, x-rays and scans, and pathology results
- Results of tests to monitor for side effects including hearing tests, heart tests, lung tests, learning ability
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

What will your or your child’s protected health information be used for?

The main reason to use your or your child’s health information is to be able to conduct research into PPB treatments and into scientific, biologic research on PPB. PPB is a very rare malignant disease in the lung of young children. It occurs in three forms: Types I, II, and III PPB. Because it is so rare, consistent treatment of a large group of children has never occurred, and treatment success is therefore very difficult to judge. In addition, PPB appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment Study has three purposes:

(4) For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease in the chest. This study collects information on treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

(5) For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed necessary.
necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

(6) To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on PPB children and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store PPB tissue of PPB children.

In addition to these PPB research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

Who may disclose your/your child’s protected health information to the researchers?

If you agree to your child’s participation in this PPB study, the study researchers and their staff may obtain your or your child’s protected individual health information from the hospital and clinic where your child is treated.

With whom would the protected health information be shared?

Your/your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child’s hospital who not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital

What is the potential for re-disclosure of your/your child’s protected health information?

All reasonable efforts will be used to protect the confidentiality of your or your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your or your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your or your child’s confidentiality will be compromised.
What happens if I do not sign this permission form?

If you do not sign this permission form, your child will not be a part in this PPB research study for which your child is being considered.

For how long will you/your child’s protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

What are your or your child’s rights after signing this Authorization form?

You/your child have the right to withdraw from participating in this research. You have the right to revoke in writing your permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your permission to conduct the research and related activities such as oversight. Even if you revoke your permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If you wish to withdraw your permission, contact the investigator and you will be asked to complete a written form.

You have the right to choose not to sign this form. If you decide not to sign, your child will not participate in this PPB research. Refusing to sign will not affect the current or future care you/your child receives at your treatment institution and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you/your child choose to share private health information with anyone not directly related to this research, the federal law designed to protect your privacy may no longer protect the shared information.

What are you/your child’s rights to access your/your child’s protected health information?

Subject to certain legal limitations, you have the right to access your child’s protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. You may access this information only after the study analyses are complete. To request this information, you will need to contact your child's doctor or the Institutional Review Board at your child's hospital. Findings from future research using material stored in the tissue bank established in this study (PPB tissue from your child will not be available to you.

By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this PPB study to use and disclose your/your child’s protected health information for the purposes described above. You also permit you/your child’s doctors and other health care providers to disclose your/your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at your child’s hospital.
CERTIFICATIONS AND SIGNATURE SECTION

I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed.

Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject) OR Research Subject’s Authorized Representative (such as Parent or Guardian) Date

Printed name of Research Subject’s Authorized Representative Representative’s relationship to Research Subject (for example: “mother” or “father” or “guardian”)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):
TAking part in genetic research: issues to consider

You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

Considering possible benefits
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

Considering possible risks
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child's point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

Insurance coverage
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

Employment or other qualification decisions
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

Emotional effects of genetic information
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
• what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
• if the researcher will keep other information with the sample
• if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
• What is the purpose of the study?
• What is my doctor’s involvement in the study?
• Who is paying for the study?
• Will I be able to get the information from the genetic testing?
• Will anyone else get the information from the genetic testing?
• Will the information from the study help me or my child?
• Will the information from the study help other people with this disease or condition?
• How are the costs of the study being paid, and will my insurance company be billed?
• Will the information be in my or my child’s medical record?
• What will happen to the sample after the study is done, and do I have any control of that?
• Will any other information be kept with the sample?
• Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child’s physician if you have questions or concerns. You may also contact Children’s Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child’s care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
HOW IS TISSUE USED FOR RESEARCH? WHAT YOU NEED TO KNOW

You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer's. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your age and gender
Your racial or ethnic group
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
Treatment you have received
Your family history
Your medical history

How is my privacy protected?
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

What are the risks to me if I give my tissue to research?
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

Can I change my mind?
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

What if I have more questions?
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
International Pleuropulmonary Blastoma Treatment and Biology Registry

NOTICE OF PRIVACY PRACTICES

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry’s legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to “you” or “your” in this Notice, we refer to the patient. When we refer to types of disclosures of information to “you,” we mean disclosures to the patient, the patient’s guardian, or the person legally authorized to receive information about the patient.

YOUR PRIVACY RIGHTS

Confidential communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke your written permission (authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

This Treatment Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

OTHER USES AND DISCLOSURES

Research: This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain
files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small. In some cases, where there is only a minimal risk to your privacy (for example, a research project comparing the treatment and outcome of all patients who received chemotherapy for PPB) we may disclose information about you without your written authorization. We will only disclose information about you for research without your authorization when the approval process determines that there is only a minimal risk to your privacy, and we have initiated steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

**Correspondence:** If you have indicated on the consent form that yes, you will allow the PPB Treatment and Biology Registry to contact you with information about new studies or other Registry services that may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this contact could be by leaving messages on a home answering machine or voice mail, by email or by the Postal Service.

**Other uses and disclosures:** Disclosures of health information not covered by this Notice or the laws that apply to PPB Treatment and Biology Registry will be made only with your written permission.

**FOR MORE INFORMATION**

If you want more information about your privacy rights, are concerned that the PPB Treatment and Biology Registry has violated your privacy rights, or you disagree with a decision that we made about access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry  
Children’s Hospitals and Clinics of Minnesota  
2525 Chicago Avenue South  
Minneapolis, MN 55404  
(612) 813-7115  
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children’s and you will not be retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights  
U.S. Department of Health and Human Services  
233 North Michigan Avenue, Suite 240  
Chicago, IL 60601  
(312) 886-2359 or 1-800-368-1019  
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes will apply to information we already have about you and information we receive about you in the future. We will provide an updated Notice to you when you request one. We will also post the most current Notice in public areas and on the PPB Treatment and Biology Registry Children’s Web site at www.ppbregistry.org

**The effective date of this Notice is May 8, 2009.**
Appendix IV – D: Types II and III PPB - Sample Consenting Documents
Types II and III PPB - Sample Informed Consent

Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry

PPB Treatment and Biology Registry Office
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN  55404   USA

RESEARCH CONSENT FORM –Types II and III PPB

INTRODUCTION
You are being asked to participate in a childhood cancer research study called a Treatment and Biology Registry; it is for children with the rare childhood lung tumor called pleuropulmonary blastoma (PPB). A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue) from patients with PPB. To participate, your agreement is necessary, but it is your choice. You are being asked to participate because your child has been diagnosed with Type II or Type III PPB.

▪ If you are a parent or legal guardian of a child who may be included in this research study, your permission is required for your child to be included.

▪ If you are the PPB patient and are old enough to consent to treatment without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.

▪ Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (generally, children ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

Part 1: Collecting data on children with Types II and III PPB and on their treatment. Children diagnosed with Types II or III PPB will be treated according to decisions at their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

Part 2: The second part of this study involves research into the biology of PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens of the tumor specimens for biological research.

Your doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your health care team. If you have any questions, you can ask your doctor or members of the Registry staff for more explanation.
This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from many countries. The research is coordinated by The International PPB Registry based at Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and Children's Hospitals of Washington University, St Louis, Missouri USA; and Children’s National Medical Center, Washington, D. C., USA.

WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?
You are being asked to take part in this study because your child has a rare malignant (cancerous) tumor called pleuropulmonary blastoma (PPB).

3. What is PPB and What are Types II and III PPB? PPB is a very rare tumor. It arises in tissue called “pleura” (pleura covers the inside of the chest cavity and also covers the surface of the lung); PPB can also arise in the “pulmonary” tissue, which is the lung itself. PPB is usually a cancer of young children, under age 72 months, but it may occur in older children. PPB is not related to the lung cancers which occur in adults.

There are three forms of PPB called Types I, II, and III PPB. Types II and III PPB are quite serious forms of childhood cancer. Types II and III PPB can spread to other parts of the body and special x-ray tests (imaging studies) are used to evaluate this.

4. Treatment of Types II and III PPB: Children with Types II and III PPB require surgery, chemotherapy and perhaps radiation therapy for treatment. It is not known what chemotherapy drugs and schedule of drugs are the best for Types II and III PPB. The reason for this is that PPB is very rare. No large group of children with Types II or III PPB has ever been collected together to determine what treatments work best.

This research study suggests surgery as complete as possible for Types II and III PPB. Sometimes surgery to remove the tumor is not done until chemotherapy has been used to shrink the tumor. Your child’s doctor will decide what chemotherapy drugs and schedule to recommend for treatment of your child. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

This Registry will collect information about how children with Types II and III PPB cases are treated. After enough cases have been collected and enough time has passed to learn how the children have done, the results will be made available to help doctors learn what therapies may be helpful for Types II and III PPB.

3. PPB Biology and Genetics: In 30-40% of cases, children with PPB or their family members have other medical conditions. One of these conditions is lung cysts which may develop into serious cancers. The evolution of lung cysts into serious solid tumors and the familial predisposition to certain illnesses is called the “biology of PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes some family members to PPB or other conditions and may be passed from generation to generation. A mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB cases have this mutation and how it may cause the disease.

The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.
WHAT DOES THE TREATMENT AND BIOLOGY REGISTRY INVOLVE?
Study Part 1: Collection of Data on Treatment of Types II and III PPB:

There are three major ways to treat cancer and PPB:

- **Surgery** to remove cancer tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells.
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells.

Types II and III PPB tumors often affect large areas of the lung and chest cavity; these PPBs cannot be removed totally by surgery. Standard (usual) treatment around the world for children with Types II and III PPB is surgery and chemotherapy, and sometimes radiation therapy. Instead of major surgery, large tumors are sometimes sampled (biopsied) first; then chemotherapy is used to shrink the tumor; then surgery is used to try to remove remaining tumor. For chemotherapy, there are many different anti-cancer drugs and many possible combinations of these drugs. Around the world, there is no standard combination or standard schedule of anti-cancer drugs for treatment of Types II and III PPB.

Children in this study will have surgery to try to remove the PPB (or a biopsy for diagnosis first with surgery later). Then your child’s doctor and his or her colleagues will decide what chemotherapy drugs and schedule to use. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose. Your child’s doctors will also decide how much surgery should be recommended to remove the PPB tumor and whether radiation therapy should be used.

This research will collect information on how children with Types II and III PPB are treated and what is their outcome.

Study Part 2: Research into PPB Biology:

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB. This study asks for permission to collect family medical history information, to store excess portions of the child’s Type II or III PPB tumor.

WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?
Study Part 1: Types II and III PPB are very rare and there is no established “standard” or “best” therapy. Around the world, children with PPB have been treated according to decisions made case-by-case over many years in many different hospitals by many different physicians. No treatment has been tested in a large group of Types II and III PPB patients. The goal of this research study is to collect treatment information for Type II and III PPB children and to try to learn how well certain treatments work. Future treatments can be compared to this treatment in order to measure improvements.

Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

In summary, the goals of this Treatment and Biology Registry are:

1) To collect data on treatment of children with Types II and III PPB and to learn the success rates of different treatments.
2) To collect family medical histories and to collect and save Types II and III PPB tumor samples from the PPB child in order to learn more about the biology of PPB and genetic factors in PPB.
HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
We estimate that about 20-40 Type II or III PPB patients per year will be collected in this Registry.

WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?
Study Part 1. Treatment of Types II and III PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: how much surgery and what chemotherapy medications and schedule to use, and whether to recommend radiation therapy. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

This research will collect information about your child and on how the Type II or III PPB was treated. This project also involves collecting x-rays and tissue from surgery to review and confirm the diagnosis of Type II or III PPB.

Study Part 2. Biology and Genetics of PPB: The biology and genetic studies of this research involve the following biological samples:

After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies.

In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.

HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?
Your child will be followed indefinitely in order to determine the outcome of the Type II or III PPB.

PPB tumor tissue from the time of initial or subsequent biopsy or surgery will be saved indefinitely to be used for research into causes and treatment of PPB.

CAN MY CHILD STOP BEING IN THIS STUDY?
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)

WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with
this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child's medical data in the Registry will help physicians and researchers learn more about PPB and its treatment. The information may be helpful in the treatment of PPB in the future. Also, study of biologic specimens in this Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat PPB more successfully.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of Types II and III PPB patients for evaluation of the results of their treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or hospital.

HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?
When a childhood cancer research study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with PPB are to be treated (your child’s doctor and his or her colleagues make those decisions), so it is not mandatory that this Registry has been reviewed and approved at your child’s hospital. Even though it may not be mandatory, some hospitals do choose to formally review a project like this.

This PPB Treatment and Biology Registry project has been approved at the children’s hospitals in Minnesota, Missouri, and Washington, D.C. who are coordinating the research.

Regardless of whether your child’s doctor and hospital have specifically approved this research project, your consent to participate is required. Many institutions encourage parents to consider participation in Registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.

The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.
WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

WHAT ARE MY RIGHTS IF I TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at your local hospital will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS REGISTRY?
You can talk to your local doctor about any questions or concerns you have about this research. Contact your doctor __________________ [name(s)] at __________________ [telephone number]. Your physician may direct you to a local Research or Ethics Board administrator at your hospital who can also help you. You may also choose to discuss participation with support personnel at your child’s hospital, such as social workers or family support counselors.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813- 7115 or krisann.schultz@childrensmn.org) You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (612) 813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES
You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

Part 1: Collection of Information on Type II and III PPB Treatment

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I agree to have my child be a part of the Treatment and Biology Registry. Part 1: Collection of Information on Types II and III PPB Treatment.

PATIENT’S NAME __________________________________________

________________________________
Print

Parent/legal guardian ___________________________ ___________________________

Print name               Signature

Relationship to patient: __________________ DATE __________________________

Please also answer this question:
Researchers studying PPB would like your permission to be able to contact you in the future if new PPB research topics are identified for which your participation would be helpful.

Do you agree to be contacted in the future about additional, special PPB research studies?

YOU DO NOT NEED TO AGREE TO THIS.

_____ I agree to be contacted in the future  _____ I do not agree to be contacted in the future

IF YOU AGREE:

Name: __________________________________________

Address: __________________________________________

_________________________________________________________________________

City, State, Postal/Zip Code: __________________________________________

Telephone Number: __________________________________________

Email address: __________________________________________

_________________________________  ________________________
Physician/Researcher obtaining consent  Date
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB and possible genetic factors which may be responsible for some cases of PPB. These research activities are separate from collecting data on how Types II and III PPB are treated.

We ask that the PPB patient and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the collection of Types II and III PPB Treatment, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in these studies without taking part in Part 1 on Types II and III PPB Treatment.)

WHAT DOES THIS PPB BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:

4. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.

5. To save leftover PPB tumor tissue (if available) from your child’s biopsy and/or surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies.

Specimens saved in this Biology Registry will be used to learn many details about PPB cancer cells and any normal cells that might surround the cancer cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how the cancer is different from normal tissue. DNA from tumor tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s tumor tissue will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for research into familial patterns of PPB and related diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this Treatment and Biology Registry.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give
them your name, address, phone number, or any other information that will let the researchers know who you are.

Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

**HOW LONG WILL SPECIMENS BE SAVED FOR BIOLOGY RESEARCH?**

Tumor tissue and family medical histories will be saved indefinitely.

**CAN MY CHILD OR I STOP BEING PART OF THIS BIOLOGY REGISTRY?**

Yes. You can inform the Treatment and Biology Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

**ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS BIOLOGY RESEARCH?**

You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB. It is possible that your child’s doctor or hospital is doing some biology research on tumors and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

**ARE THERE ANY BENEFITS?**

There is no direct benefit to you or your child from participating in the PPB Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.

**ARE THERE ANY RISKS?**

The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private. Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.

**WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?**

If you have any questions, please talk to your doctor or other patient support personnel at your child’s hospital.
You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org). You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (621) 813-7646 in Minneapolis, Minnesota USA.

A document called "How is Tissue Used for Research?" is attached to this consent form.

**MAKING YOUR CHOICE ABOUT PARTICIPATING IN PPB BIOLOGY REGISTRY**

One parent can authorize participation of a child in Part 2: the PPB Biology Research Registry. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s PPB care.

After reading each sentence, circle "Yes" or "No" and write your signature and date in the spaces provided.

**Consent for Participation in PPB Biology Registry Research:**

- **Family Medical History and Saving Tumor Tissue for Research**

1. Your Child’s Participation in PPB Biology Registry
   
   I agree to allow my child’s family medical history to be collected. I also agree to allow any leftover PPB tumor tissue (if available) from my child to be saved for research studies related to PPB.

   Yes  No

   Signature of parent/guardian  relationship to patient

   ______________________________

   Date

---

**Physician/Researcher obtaining consent**

**Date**

**IRB#**

**Initial IRB Approval:**
Types II & III PPB Sample Informed Assent for Participation in The International PPB Treatment and Biology Registry

Name: ____________________________

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Registry Office:
International PPB Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN  55404   USA

Assent Form for Child or Adolescent Ages 7-17 with Type II or Type III PPB

We are asking you to take part in a research study because you have pleuropulmonary blastoma (PPB). PPB is a rare type of cancer in the lung. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about PPB and how to treat it. We will do this by collecting records on how doctors treat children with Types II & III PPB. Based on past experiences, the Registry makes suggestions on how PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want your permission as well. Children and teens with Types II and III PPB will be treated with surgery and chemotherapy. Some may also need to receive radiation therapy. Chemotherapy is a type of strong medicine that destroys cancer cells. Radiation therapy uses strong x-rays to destroy cancer cells. Chemotherapy and radiation therapy can also cause side effects that could make you temporarily feel sicker.

As part of this study, information about your illness and how you respond to treatment is sent to the main PPB Study research office. Doctors from around the world want to share information about treating children and teenagers who have PPB. By sharing information, we can more quickly learn the best ways to treat cancer. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also receive a sample of the tumor that was removed from your chest so that they can learn in the future about how and perhaps why PPB cancers exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it.

Your mother or father or guardian can help you decide whether to agree to this scientific study. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.
**Please answer the following question by circling either YES or NO and entering your initials.**

1. My tissue may be sent to the PPB Study office to be used in research about PPB.
   - YES  
   - NO  
   - Initials ______

2. My leftover tissue may be kept by the PPB Study office for use in future research studies.
   - YES  
   - NO  
   - Initials ______

3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.
   - YES  
   - NO  
   - Initials ______

I agree to take part in this study.

---

**Assent by child/adolescent**  
**Date**

**To the professional:**
If the child *does not* sign the form but you believe the child has *actively assented*, please document on this form. State the specific behaviors (*child shook head yes, child said “OK” after I described procedure, etc.*).

---

**Physician/Researcher obtaining consent**  
**Date**

**IRB#**  
**Initial IRB Approval:**
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________

Please print (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________

Hospital Name: ____________________________________________________

The following information is requested:

 Hospital discharge summaries
 Pathologist’s reports on surgical specimens, bone marrow, CSF
 Surgical/operative reports
 Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
 Treatment records (chemotherapy, radiation therapy, including chemo roadmaps)
 Consultations
 Pediatric Oncology CLINIC records
 Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
 Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.
E-mail: gretchen.williams@childrensmn.org

Telephone: 612 813 7115
Fax: 612 813 7108

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

____________________________________________    _____________________________
Printed Name of Parent or Guardian      Date Signed

____________________________________________    _____________________________
Signature of Parent or Guardian      Relationship to Patient

_______________________________________________________________________________________________________
Address             City       State          Zip Code

_____________________________________     _____________________________
Parent or Guardian Home Phone      Parent or Guardian Work Phone
The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects you and your child’s individually identifiable health information (protected health information). The privacy law requires you or your child to sign an authorization in order for researchers to be allowed to use or disclose your/your child’s protected health information for research purposes in the study entitled International PPB Treatment Study.

What protected health information may be used or disclosed?

Your/your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, tumor measurement, x-rays and scans, and pathology results
- Results of tests to monitor for side effects including hearing tests, heart tests, lung tests, learning ability
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

What will your or your child’s protected health information be used for?

The main reason to use your or your child’s health information is to be able to conduct research into PPB treatments and into scientific, biologic research on PPB. PPB is a very rare malignant disease in the lung of young children. It occurs in three forms: Types I, II, and III PPB. Because it is so rare, consistent treatment of a large group of children has never occurred, and treatment success is therefore very difficult to judge. In addition, PPB appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment Study has three purposes:

4. For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease in the chest. This study collects information on treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

5. For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed...
necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

6. To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on PPB children and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store PPB tissue.

In addition to these PPB research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

Who may disclose your/your child’s protected health information to the researchers?

If you agree to your child’s participation in this PPB study, the study researchers and their staff may obtain your or your child’s protected individual health information from the hospital and clinic where your child is treated.

With whom would the protected health information be shared?

Your/your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child’s hospital who not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital

What is the potential for re-disclosure of your/your child’s protected health information?

All reasonable efforts will be used to protect the confidentiality of your or your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your or your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your or your child’s confidentiality will be compromised.
**What happens if I do not sign this permission form?**

If you do not sign this permission form, your child will not be a part in this PPB research study for which your child is being considered.

**For how long will you/your child’s protected health information be used or shared with others?**

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

**What are your or your child’s rights after signing this Authorization form?**

You/your child have the right to withdraw from participating in this research. You have the right to revoke in writing your permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your permission to conduct the research and related activities such as oversight. Even if you revoke your permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If you wish to withdraw your permission, contact the investigator and you will be asked to complete a written form.

You have the right to choose not to sign this form. If you decide not to sign, your child will not participate in this PPB research. Refusing to sign will not affect the current or future care you/your child receives at your treatment institution and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you/your child choose to share private health information with anyone not directly related to this research, the federal law designed to protect your privacy may no longer protect the shared information.

**What are you/your child’s rights to access your/your child’s protected health information?**

Subject to certain legal limitations, you have the right to access your child’s protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. You may access this information only after the study analyses are complete. To request this information, you will need to contact your child's doctor or the Institutional Review Board at your child's hospital. Findings from future research using material stored in the tissue bank established in this study (PPB tissue from your child) will not be available to you.

By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this PPB study to use and disclose your/your child’s protected health information for the purposes described above. You also permit you/your child’s doctors and other health care providers to disclose you/your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at your child’s hospital.
CERTIFICATIONS AND SIGNATURE SECTION

I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed.

Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject)  OR Research Subject’s Authorized Representative (such as Parent or Guardian)  Date

Printed name of Research Subject’s Authorized Representative  Representative’s relationship to Research Subject (for example: “mother” or “father” or “guardian”)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):
TAKING PART IN GENETIC RESEARCH: ISSUES TO CONSIDER

You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

Considering Possible Benefits
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

Considering Possible Risks
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child's point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

Insurance Coverage
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

Employment or Other Qualification Decisions
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

Emotional Effects of Genetic Information
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
- what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
- if the researcher will keep other information with the sample
- if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
- What is the purpose of the study?
- What is my doctor’s involvement in the study?
- Who is paying for the study?
- Will I be able to get the information from the genetic testing?
- Will anyone else get the information from the genetic testing?
- Will the information from the study help me or my child?
- Will the information from the study help other people with this disease or condition?
- How are the costs of the study being paid, and will my insurance company be billed?
- Will the information be in my or my child’s medical record?
- What will happen to the sample after the study is done, and do I have any control of that?
- Will any other information be kept with the sample?
- Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child's physician if you have questions or concerns. You may also contact Children's Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child's care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
HOW IS TISSUE USED FOR RESEARCH? WHAT YOU NEED TO KNOW

You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer's. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your gender and age
Your racial or ethnic group
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
Treatment you have received
Your family history
Your medical history.

**How is my privacy protected?**
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

**What are the risks to me if I give my tissue to research?**
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

**Can I change my mind?**
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

**What if I have more questions?**
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
NOTICE OF PRIVACY PRACTICES

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry’s legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to “you” or “your” in this Notice, we refer to the patient. When we refer to types of disclosures of information to “you,” we mean disclosures to the patient, the patient’s guardian, or the person legally authorized to receive information about the patient.

YOUR PRIVACY RIGHTS

Confidential communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke your written permission (authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment and Biology Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

This Treatment and Biology Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

OTHER USES AND DISCLOSURES

Research: This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain
files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small. In some cases, where there is only a minimal risk to your privacy (for example, a research project comparing the treatment and outcome of all patients who received chemotherapy for PPB) we may disclose information about you without your written authorization. We will only disclose information about you for research without your authorization when the approval process determines that there is only a minimal risk to your privacy, and we have initiated steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

**Correspondence:** If you have indicated on the consent form that yes, you will allow the PPB Treatment and Biology Registry to contact you with information about new studies or other Registry services that may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this contact could be by leaving messages on a home answering machine or voice mail, by email or by the Postal Service.

**Other uses and disclosures:** Disclosures of health information not covered by this Notice or the laws that apply to PPB Treatment and Biology Registry will be made only with your written permission.

**FOR MORE INFORMATION**

If you want more information about your privacy rights, are concerned that the PPB Treatment and Biology Registry has violated your privacy rights, or you disagree with a decision that we made about access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry  
Children’s Hospitals and Clinics of Minnesota  
2525 Chicago Avenue South  
Minneapolis, MN 55404  
(612) 813-7115  
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children’s and you will not be retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights  
U.S. Department of Health and Human Services  
233 North Michigan Avenue, Suite 240  
Chicago, IL 60601  
(312) 886-2359 or 1-800-368-1019  
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes will apply to information we already have about you and information we receive about you in the future. We will provide an updated Notice to you when you request one. We will also post the most current Notice in public areas and on the PPB Treatment and Biology Registry Children’s Web site at www.ppbregistry.org

**The effective date of this Notice is May 8, 2009.**
NOTE: This is the Consent only

No HIPAA, Assent, or attachments translations included
PPB tipo II y III – Consentimiento informado

Nombre del participante (en letra de imprenta)

Registro internacional de tratamiento y aspectos biológicos sobre el blastoma pleuropulmonar

Oficina del Registro de tratamiento y aspectos biológicos sobre el PPB
Registro Internacional del PPB
Children’s Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN 55404 EE. UU.

FORMULARIO DE CONSENTIMIENTO PARA UNA INVESTIGACIÓN - PPB tipo II y III

INTRODUCCIÓN

Se le pide que participe en un estudio de investigación sobre cáncer infantil llamado Registro de tratamiento y aspectos biológicos. Está dirigido a niños con un tumor en el pulmón poco común llamado blastoma pleuropulmonar (pleuropulmonary blastoma, PPB). Un Registro de tratamiento y aspectos biológicos implica la obtención de información clínica y muestras biológicas (tejido tumoral y saliva o sangre) de pacientes con PPB y de sus padres. Para participar, es necesario obtener su aceptación, aunque usted elige. Se le pide que participe porque a su hijo se le ha diagnosticado PPB tipo II o III.

- Si usted es el padre o tutor legal de un niño que puede incluirse en este estudio de investigación, necesita su permiso para que el niño sea incluido.

- Si usted es el paciente con PPB y es lo suficientemente mayor como para dar el consentimiento para recibir el tratamiento sin el permiso de sus padres (la mayoría de edad en la mayoría de las instituciones es 17 años), la frase “su hijo” en este formulario de consentimiento se refiere a usted.

- En función de las prácticas del hospital de su hijo, si su hijo es lo suficientemente mayor como para comprender algunos aspectos de la atención médica (generalmente, niños de 7 a 17 años), puede requerirse la “aceptación” (el acuerdo) de su hijo, además del consentimiento del padre o la madre.

Este Registro de tratamiento y aspectos biológicos tiene dos partes:

Parte 1: Obtención de datos sobre niños con PPB tipo II y III, y sobre su tratamiento. Los niños con un diagnóstico de PPB tipo II o III recibirán tratamiento de acuerdo con las decisiones tomadas en su propio hospital. Se obtendrá información sobre el tratamiento administrado y la evolución del niño a partir de entonces.

Parte 2: La segunda parte de este estudio implica investigar la biología del PPB y las posibles causas genéticas. Esto implica obtener información sobre los antecedentes médicos de la familia y obtener muestras del tumor y de saliva, y/o muestras de sangre para realizar una investigación biológica.

El médico puede explicarle este proyecto de investigación. Usted puede elegir que su hijo participe o que no lo haga. Su hijo puede participar en la parte 1 o en la parte 2, o en las dos partes. Las investigaciones como esta incluyen solamente a las personas que eligen participar. Dedique el tiempo que necesite para...
tomar una decisión sobre la participación. Puede analizar su decisión con amigos, familiares u otros consejeros de confianza. También puede analizarla con el equipo de atención médica. Si tiene alguna pregunta, puede hacérsela al médico o a los integrantes del personal del Registro para obtener una explicación más detallada.

Un grupo de centros oncológicos infantiles de muchos países realiza este Registro de tratamiento y aspectos biológicos. Coordina esta investigación The International PPB Registry con sede en Children’s Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota, EE. UU.; Barnes-Jewish and Children's Hospitals of Washington University, St Louis, Missouri, EE. UU.; y Children’s National Medical Center, Washington, D. C., EE. UU.

¿EN QUÉ CONSISTE EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
Se le pide que participe en este estudio porque su hijo tiene un tumor maligno (canceroso) poco común llamado blastoma pleuropulmonar (PPB).

1. ¿Qué es el PPB y qué son los tipos II y III del PPB? El PPB es un tumor muy poco común. Aparece en el tejido que se llama “pleura” (la pleura cubre el interior de la cavidad torácica y también cubre la superficie del pulmón). El PPB también puede aparecer en el tejido “pulmonar”, que es el pulmón en sí. El PPB es un cáncer que habitualmente aparece en niños pequeños, menores de 72 meses de vida, pero puede aparecer en niños mayores. El PPB no está relacionado con los tipos de cáncer de pulmón que afectan a los adultos.

Existen tres formas de PPB llamadas PPB tipo I, II y III. El PPB tipo II y tipo III son formas bastante graves de cáncer infantil. El PPB tipo II y III puede diseminarse a otras partes del cuerpo y, para evaluar esto, se utilizan pruebas radiológicas especiales (estudios con obtención de imágenes).

2. Tratamiento para el PPB tipo II y III: Los niños con PPB tipo II y III requieren cirugía, quimioterapia y quizás radioterapia como tratamiento. No se sabe qué fármacos quimioterapéuticos y programa de fármacos son mejores para el PPB tipo II y III. El motivo de esto es que el PPB es una enfermedad muy poco común. Nunca se ha formado un grupo grande de niños con PPB tipo II o III para determinar qué tratamientos funcionan mejor.

Este estudio de investigación sugiere una cirugía, lo más completa posible, para el PPB tipo II y III. A veces, no se realiza la cirugía para extirpar el tumor hasta que se ha aplicado quimioterapia para reducir su tamaño. El médico de su hijo decidirá qué fármacos quimioterapéuticos y programa recomendará para el tratamiento de su hijo. El médico de su hijo puede considerar la posibilidad de usar una pauta de quimioterapia preparada para este Registro de tratamiento y aspectos biológicos, pero no hay información que permita determinar si esta pauta es mejor que otra quimioterapia que el médico pueda elegir.

En este Registro, se obtendrá información sobre el modo en que se tratan los casos de niños con PPB tipo II y III. Después de haber obtenido suficientes casos y de que haya transcurrido suficiente tiempo para saber cómo les ha ido a los niños, los resultados se pondrán a disposición para que los médicos sepan qué terapias pueden resultar útiles para el PPB tipo II y III.

3. Biología y genética del PPB: En el 30% al 40% de los casos, los niños con PPB o sus familiares tienen otras afecciones. Una de estas afecciones son quistes en los pulmones, que pueden generar tipos de cáncer graves. La evolución de los quistes de pulmón en tumores sólidos graves y la predisposición familiar a determinadas enfermedades se denomina “biología del PPB”. Esto sugiere que una anormalidad genética, como una alteración en el ADN (una mutación), predispone a algunos integrantes de la familia al PPB o a otras afecciones, y puede transmitirse de una generación a otra.
Se ha detectado una mutación (anormalidad en el ADN) en algunos familiares con PPB, pero se necesita seguir investigando para comprender qué cantidad de casos de PPB presentan esta mutación y cómo puede ella causar la enfermedad.

Las enfermedades asociadas con el PPB son quistes en los pulmones, otros casos de PPB, quistes en los riñones, algunos tipos de cáncer infantil, algunos tumores en los ovarios y los testículos, pequeños pólipos intestinales y una serie de afecciones muy poco comunes más. Se deben realizar investigaciones para determinar una lista completa de afecciones asociadas al PPB. No todas estas afecciones son cáncer. La mayoría de las personas pertenecientes a familias con PPB son normales.

¿QUÉ IMPLICA EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
Parte 1 del estudio: Obtención de datos sobre el tratamiento del PPB tipo II y III: Existen tres maneras principales de tratar el cáncer y el PPB:

- **Cirugía** para extirpar los tumores cancerosos.
- **Quimioterapia**, o el uso de fármacos anticancerosos, para detener el crecimiento de las células cancerosas.
- **Radioterapia**, o el uso de rayos X de alta energía u otros tipos de radiación, para destruir las células cancerosas.

Los tumores del PPB tipo II y III a menudo afectan grandes áreas del pulmón y de la cavidad torácica. Estos PPB no se pueden extirpar mediante cirugía en su totalidad. El tratamiento estándar (habitual) en todo el mundo para niños con PPB tipo II y III es la cirugía y la quimioterapia y, a veces, la radioterapia. En lugar de una cirugía mayor, a veces, primero se obtienen muestras de los tumores grandes (se les realiza una biopsia). Luego, se utiliza quimioterapia para reducir el tamaño del tumor y, a continuación, se realiza una cirugía para intentar extirpar el resto del tumor. En el caso de la quimioterapia, existen muchos fármacos anticancerosos y muchas combinaciones posibles de estos fármacos. No existe ninguna combinación estándar ni programa estándar de fármacos anticancerosos en ninguna parte del mundo para el tratamiento del PPB tipo II y III.

Los niños que participan en este estudio deberán realizarse una cirugía para intentar extirpar el PPB (o, primero, una biopsia para el diagnóstico y una cirugía más adelante). Luego, el médico de su hijo y sus colegas decidirán qué fármacos quimioterapéuticos y qué programa utilizarán. El médico de su hijo puede considerar la posibilidad de usar una pauta de quimioterapia preparada para este Registro de tratamiento y aspectos biológicos, pero no hay información que permita determinar si esta pauta es mejor que otra quimioterapia que el médico pueda elegir. Los médicos de su hijo también decidirán qué grado de cirugía debe recomendarse para extirpar el tumor del PPB y si se debe usar radioterapia.

En esta investigación, se obtendrá información sobre el tratamiento que reciben los niños con PPB tipo II y III, y sobre el resultado de esta.

Parte 2 del estudio: Investigación sobre la biología y la genética del PPB:

Es mucho lo que se debe investigar sobre los antecedentes médicos familiares, sobre la biología del PPB y sobre los factores genéticos que podrían causar algunos casos de PPB. En este estudio, se pide permiso para obtener información sobre los antecedentes médicos familiares con el fin de guardar partes del tumor del PPB tipo II o III del niño, y para obtener y guardar saliva o sangre del niño, de la madre y del padre a fin de usarlos en investigaciones.

¿POR QUÉ SE CREA EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
Parte 1 del estudio: El PPB tipo II y III es muy poco común y no existe una terapia “estándar” o “mejor” establecida. Durante muchos años, muchos médicos diferentes en muchos hospitales diferentes han tratado...
a niños con PPB en todo el mundo en función de decisiones tomadas caso por caso. No se ha evaluado ningún tratamiento en un grupo grande de pacientes con PPB tipo II y III. El objetivo de este estudio de investigación es obtener información sobre el tratamiento del PPB tipo II y III en niños e intentar determinar qué tan bien funcionan determinados tratamientos. Los tratamientos futuros posiblemente se comparen con este tratamiento para evaluar las mejoras.

Parte 2 del estudio: Hay mucho por aprender sobre la biología y la genética del PPB y de las afecciones asociadas. En este estudio, se reúnen los antecedentes médicos familiares, y se establece una serie de muestras de pacientes con PPB y sus padres para investigación con el fin de intentar responder algunas de estas preguntas.

En resumen, los objetivos de este Registro de tratamiento y aspectos biológicos son:

1) Obtener datos sobre el tratamiento de niños con PPB tipo II y III, y conocer las tasas de éxito de los diferentes tratamientos.

2) Obtener los antecedentes médicos familiares, y obtener y guardar muestras de tumores de PPB tipo II y III, así como muestras de saliva o sangre del niño con PPB y de la madre y el padre para obtener más información sobre la biología del PPB y los factores genéticos involucrados en el PPB.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
Calculamos que en este Registro, se obtendrá información sobre 20 a 40 pacientes con PPB tipo II o III por año.

¿QUÉ SUCEDERÁ SI MI HIJO PARTICIPA EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
Parte 1 del estudio. Tratamiento para el PPB tipo II y III: Ya sea que su hijo participe en esta investigación o no, los médicos de su hijo emplearán su mejor juicio para evaluar y tratar a su hijo: qué grado de cirugía, y qué medicamentos quimioterapéuticos y programa usar, y si es necesario recomendar radioterapia. El médico de su hijo puede considerar la posibilidad de usar una pauta de quimioterapia preparada para este Registro de tratamiento y aspectos biológicos, pero no hay información que permita determinar si esta pauta es mejor que otra quimioterapia que el médico pueda elegir.

En esta investigación, se obtendrá información sobre su hijo y sobre el modo en que se trató el PPB tipo II o III. Este proyecto también implica obtener radiografías y tejido de la cirugía para revisar y confirmar el diagnóstico de PPB tipo II o III.

Parte 2 del estudio. Biología y genética del PPB: Los estudios de biología y genética de esta investigación implican las siguientes muestras biológicas:

- Del niño con PPB:
  - Una vez cumplidos todos los requisitos de diagnóstico, se guardará parte de cualquier tejido tumoral adicional extraído en la cirugía para estudios de investigación.
  - Obtención de sangre o saliva para muestras de ADN para realizar estudios de investigación.

- De la madre:
  - Obtención de sangre o saliva para muestras de ADN para realizar estudios de investigación.
Del padre:
○ Obtención de sangre o saliva para muestras de ADN para realizar estudios de investigación.

Además, se obtendrá información sobre los antecedentes médicos familiares. Más adelante en este formulario de consentimiento, encontrará información adicional sobre la parte 2 de esta investigación.

¿CUÁNTO TIEMPO PARTICIPARÁ MI HIJO EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
A su hijo se le realizará un seguimiento de manera indefinida para determinar el desenlace del PPB tipo II o III.

El tejido tumoral del PPB obtenido en la biopsia o cirugía inicial o posterior se guardará indefinidamente para usarlo en investigaciones sobre las causas y el tratamiento del PPB. También se guardarán indefinidamente las muestras de sangre o saliva de su hijo, y de la madre y del padre, para realizar investigaciones sobre las causas, la biología y el tratamiento del PPB.

¿PUEDE MI HIJO DEJAR DE PARTICIPAR EN ESTE ESTUDIO?
Sí. Puede decidir que su hijo deje de participar en este Registro en cualquier momento. Comuníqueselo al Registro de tratamiento y aspectos biológicos, y digale al médico de su hijo que desea retirar su permiso para participar. En otras partes de este formulario de consentimiento, se incluye información de contacto. El médico de su hijo seguirá cuidando de su hijo independientemente de la decisión de retirarlo de este Registro.

(Si su hijo deja de participar en este estudio, no será posible eliminar la información del niño de los resúmenes de los datos del estudio que ya se hayan incorporado en publicaciones o presentaciones científicas; los resúmenes del estudio y las investigaciones futuras no incluirán a su hijo).

¿CUÁLES SON LOS RIESGOS PARA MI HIJO DE PARTICIPAR EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
No existen riesgos médicos específicos para su hijo por incluirlo en este Registro de tratamiento y aspectos biológicos. Su hijo recibirá la misma atención médica de los médicos y del hospital independientemente de que forme parte de este Registro. Existe un riesgo leve de que, como la historia clínica de su hijo se comparte con este Registro, pueda ocurrir una pérdida de la confidencialidad. Se toman muchas medidas para mantener toda la información personal de manera confidencial, como se describe más adelante.

¿HAY BENEFICIOS POR PARTICIPAR EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
No existe un beneficio inmediato o directo por ser incluido en este Registro de tratamiento y aspectos biológicos. Indirectamente, que se incluyan datos médicos de su hijo en el Registro ayudará a los médicos e investigadores a obtener más información sobre el PPB y su tratamiento. La información puede resultar útil para el tratamiento del PPB en el futuro. Además, el estudio de las muestras biológicas de este Registro puede mejorar el entendimiento de las causas del PPB y de las afecciones asociadas, cómo detectarlas más rápidamente, cómo prever a los integrantes susceptibles de las familias y, quizás, cómo tratar el PPB con mejores resultados.

¿QUÉ OTRAS OPCIONES TENGO SI NO PARTICIPO EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?
Puede elegir participar en esta investigación o no participar. Este Registro de tratamiento y aspectos biológicos intenta reunir a un grupo grande de pacientes con PPB tipo II y III para evaluar los resultados.
de sus tratamientos y para estudiar la biología y la genética del PPB. No hay ningún otro grupo en el mundo que esté intentando hacer esto para el PPB. La alternativa que usted tiene disponible es no participar en este Registro ni en ninguna investigación alternativa.

Si elige no participar, su decisión no tendrá ningún efecto en la atención que su hijo recibirá del médico o el hospital de su hijo.

¿HAN APROBADO EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS EL MÉDICO DE MI HIJO Y EL HOSPITAL?

Cuando un estudio de investigación sobre cáncer infantil permite explicar en detalle cómo debe tratarse una enfermedad, se obliga a cada hospital participante a revisar y aprobar el estudio antes de preguntarles a los pacientes si participarán en el tratamiento en investigación. Éste Registro de tratamiento y aspectos biológicos sobre el PPB no explica en detalle cómo deben tratarse los niños con PPB (el médico de su hijo y sus colegas toman esas decisiones), de modo que el hospital donde se atiende su hijo no tiene la obligación de revisar y aprobar este Registro. Aunque no sea obligatorio, algunos hospitales igualmente eligen revisar formalmente un proyecto como este.

Este Registro de tratamiento y aspectos biológicos sobre el PPB se ha aprobado en los hospitales pediátricos de Minnesota, Missouri y Washington, D.C., que coordinan la investigación.

Independientemente de que el médico de su hijo y el hospital hayan aprobado específicamente este proyecto de investigación, se exige su consentimiento para participar. Muchas instituciones alientan a los padres a considerar la posibilidad de participar en registros como este, para enfermedades poco comunes, porque es la única manera práctica de reunir información sobre un grupo grande de niños con una enfermedad poco común.

¿SE MANTENDRÁ PRIVADA LA INFORMACIÓN MÉDICA DE MI HIJO?

Haremos todo lo posible para asegurarnos de que se mantenga la privacidad de la información personal de la historia clínica de su hijo. Los consultorios del Registro de tratamiento y aspectos biológicos (Minnesota, Missouri y Washington, DC) mantienen archivos y datos en consultorios cerrados con llave y en computadoras protegidas con contraseña. Los nombres de los pacientes se reemplazarán en los archivos y registros informáticos con números de casos del Registro asignados aleatoriamente. Si la información de este Registro se publica o presenta en reuniones científicas, no se utilizará el nombre de su hijo ni ninguna otra información personal. No podemos garantizar la privacidad completa, pero las posibilidades de que la información personal se entregue a alguna otra persona es muy remota.

Las prácticas de privacidad de este Registro de tratamiento y aspectos biológicos se adjuntan al final de este formulario de consentimiento.

¿CUÁLES SON LOS COSTOS POR PARTICIPAR EN ESTE ESTUDIO?

No hay ningún costo por participar en esta investigación. Usted y su hijo no recibirán ningún pago por participar en este Registro de tratamiento y aspectos biológicos.

¿CUÁLES SON MIS DERECHOS SI PARTICIPO EN EL REGISTRO DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS?

La participación en este Registro de tratamiento y aspectos biológicos es voluntaria. Usted puede elegir que su hijo no participe o puede retirarlo del Registro en cualquier momento. La atención médica que recibirá su hijo en el hospital local será la misma independientemente de que usted elija o no que participe en el Registro o elija retirarlo más adelante.
¿QUIÉN PUEDE RESPONDER MIS PREGUNTAS SOBRE ESTE REGISTRO?
Si tiene preguntas o preocupaciones sobre esta investigación, puede hablar con el médico local. El médico puede derivarlo al administrador local de la investigación o del comité de ética del hospital, que también puede ayudarlo. Usted también puede elegir analizar su participación con personal auxiliar del hospital donde se atiene su hijo, como trabajadores sociales o asesores de apoyo familiar.

CONSENTIMIENTO PARA PARTICIPAR y FIRMAS
Se le pide que dé su consentimiento de forma separada para las partes 1 y 2 de este Registro de tratamiento y aspectos biológicos.

Parte 1: Obtención de información sobre el tratamiento del PPB tipo II y III

He recibido una copia de este formulario de consentimiento. He leído (o me han leído) este formulario. Entiendo la información y he recibido respuestas a mis preguntas.

Acepto que mi hijo participe en el Registro de tratamiento y aspectos biológicos, Parte 1: Obtención de información sobre el tratamiento del PPB tipo II y III.

NOMBRE DEL PACIENTE ____________________________

Nombre del sujeto

Padre/madre/tutor legal ______________________________    ___________________________

Nombre (en letra de imprenta)  Firma

Vínculo con el paciente: ____________________   FECHA _________________________

Además, responda esta pregunta:

Los investigadores que estudian el PPB desean obtener su permiso para comunicarse con usted en el futuro en caso de que se identifiquen nuevos temas de investigación sobre el PPB para los cuales su participación pudiera ser útil.

¿Acepta que se comuniquen con usted en el futuro sobre estudios de investigación sobre el PPB adicionales y especiales?

NO ESTÁ OBLIGADO A ACEPTAR ESTO.

_____ Acepto que se comuniquen conmigo en el futuro.

_____ No acepto que se comuniquen conmigo en el futuro.

SI ACEPTA:

Nombre: ___________________________________________

Dirección: ___________________________________________

Ciudad, estado, código postal: ___________________________________________

Número de teléfono: ___________________________________________

Dirección de correo electrónico: ___________________________________________

N.° del IRB: 0909-082   Aprobación inicial del IRB: 22/12/2009

Aprobación más reciente del IRB: 22/07/2015
Parte 2: Obtención y almacenamiento de muestras biológicas para investigación

“INVESTIGACIÓN BIOLÓGICA” SOBRE EL PPB

Esta sección de este formulario de consentimiento trata sobre los estudios de investigación de la biología del PPB y de los posibles factores genéticos que posiblemente sean responsables de algunos casos de PPB. Estas actividades de investigación son independientes de la obtención de datos sobre los tratamientos para los PPB tipo II y III.

Pedimos que el paciente con PPB, y la madre y el padre del niño participen en esta investigación. Usted puede participar o negarse a participar en estos estudios adicionales.

(Se puede inscribir a su hijo en la parte 1 de la obtención de datos sobre el tratamiento del PPB tipo II y III, aunque usted diga que “no” autoriza su participación en la parte 2 de la investigación sobre la biología del PPB. Opcionalmente, usted y su hijo pueden participar en estos estudios sin necesidad de participar en la parte 1 del tratamiento del PPB tipo II y III).

¿QUÉ IMPLICA ESTA INVESTIGACIÓN SOBRE LA BIOLOGÍA DEL PPB?

Le pediremos que dé su permiso para hacer lo siguiente:

1. Obtener sus antecedentes médicos familiares: registrar información médica sobre sus hijos y familiares de modo que incluya, en general, a personas de 2 a 4 generaciones de su familia.
2. Guardar tejido tumoral del PPB sobrante (si lo hubiera) de la biopsia y/o la cirugía de su hijo. Este se guardará en un banco de tejido, que es un laboratorio donde se guardan muestras del tumor y de otra clase para estudios de investigación.
3. Obtener y guardar muestras de saliva o sangre de su hijo y de cada padre biológico para realizar investigaciones.

La cantidad de saliva obtenida será aproximadamente de 2 cucharadas (30 ml) y la cantidad de sangre, de aproximadamente 2 cucharaditas (10 ml). En la mayoría de los casos, se obtendrá saliva. Se extraerá tejido tumoral del tumor extirpado durante la cirugía, después de que se hayan cumplido todos los requisitos de diagnóstico.

Las muestras guardadas en este Registro de aspectos biológicos se usarán para obtener muchos detalles sobre las células cancerosas del PPB y cualquier célula normal que pudiera encontrarse alrededor de las células cancerosas. Esto implica observar las sustancias químicas y tal vez los genes (ADN) dentro del tejido, y tratar de determinar exactamente cómo difiere el cáncer del tejido normal. Se investigará el ADN de la saliva, la sangre o el tejido tumoral para determinar si se pueden detectar cambios constantes que pudieran formar parte de la causa del PPB y de las afecciones relacionadas. Los resultados de esta investigación no se incluirán en su historia clínica o la de su hijo.

El tejido tumoral de su hijo, y las muestras de saliva y sangre de su hijo o suyas se usarán únicamente en investigaciones y no se venderán. Las investigaciones realizadas con estas muestras posiblemente ayuden a desarrollar productos nuevos en el futuro.

Antes de decidir si va a participar en este Registro de aspectos biológicos sobre el PPB, lea la siguiente información adicional:

¿POR QUÉ SE REALIZA ESTA INVESTIGACIÓN?

El PPB es un cáncer infantil poco común porque está asociado a otras afecciones del paciente o de los familiares en el 40% de los casos aproximadamente. Estos descubrimientos sugieren que en algunos casos de PPB y en algunas familias con un hijo con PPB, existe un factor genético que predispone a los familiares al PPB y a diversas afecciones relacionadas con el PPB. Todavía queda mucho por aprender
acera de los antecedentes médicos familiares, y sobre la causa del PPB y la frecuencia con la que aparece
una predisposición familiar. El objetivo de los estudios biológicos es reunir antecedentes familiares y
obtener muestras que puedan utilizarse en investigaciones sobre patrones familiares del PPB y de
enfermedades relacionadas. Los antecedentes y las muestras se guardarán indefinidamente para usarlos en
investigaciones a cargo de investigadores que posean ideas aprobadas por un comité de investigación
asociado con este Registro de tratamiento y aspectos biológicos.

Se realizarán investigaciones en varios laboratorios. Los resultados de estos estudios no afectarán el
tratamiento del PPB de su hijo directamente y, en consecuencia, los resultados de las pruebas no formarán
parte de la historia clínica de su hijo. En el futuro, las personas que realizan investigaciones con estas
muestras posiblemente necesiten obtener más información sobre su salud. Si bien este Registro puede
entregarles ciertos detalles sobre su salud o la salud de su hijo, no les dará su nombre, dirección, número
de teléfono ni ninguna otra información que les permita a los investigadores conocer su identidad.

Además, es importante que comprenda que, dada la naturaleza investigativa de estas pruebas, los
resultados no estarán disponibles para usted ni para los médicos del estudio.

Usted puede elegir participar en esta Investigación biológica sobre el PPB o no hacerlo. Su decisión no
afectará a la atención o al tratamiento que recibe su hijo.

¿DURANTE CUÁNTO TIEMPO SE GUARDARÁN LAS MUESTRAS PARA
INVESTIGACIONES BIOLÓGICAS?
El tejido tumoral, las muestras de saliva o sangre y los antecedentes médicos familiares se
guardarán indefinidamente.

¿PUEDO YO O PUEDE MI HIJO DEJAR DE PARTICIPAR EN ESTE REGISTRO DE
ASPECTOS BIOLÓGICOS?
Sí. Puede comunicarle al Registro de tratamiento y aspectos biológicos y/o al médico de su hijo en
cualquier momento que ya no quiere que el tejido o los antecedentes médicos se usen en este Registro de
aspectos biológicos sobre el PPB. En otras partes de este formulario de consentimiento, se incluye
información de contacto. Si decide que ya no quiere participar en esta investigación, se dejarán de usar sus
muestras o las muestras de su hijo, así como sus antecedentes o los de su hijo. Si se los ha usado antes de
esse momento y los resultados se incluyeron en resúmenes o publicaciones, no será posible eliminar
esos datos.

El médico de su hijo seguirá cuidando de su hijo independientemente de la decisión de retirarlo de
este Registro.

¿HAY ALGUNA ALTERNATIVA SI NO PARTICIPO EN ESTA INVESTIGACIÓN BIOLÓGICA?
Puede elegir participar en esta investigación o no participar. Este Registro de tratamiento y aspectos
biológicos intenta reunir a un gran grupo de participantes de la investigación y no hay ningún otro grupo
en el mundo tratando de hacer esto para el PPB. Es posible que el médico de su hijo o el hospital estén
realizando investigaciones biológicas con tumores y nosotros lo alentamos a considerar la posibilidad de
participar si esto estuviera disponible y usted decide hacerlo. La alternativa que usted tiene disponible es
no participar en este Registro ni en ninguna investigación alternativa.
¿EXISTE ALGÚN BENEFICIO?
No hay ningún beneficio directo para usted o su hijo por participar en el Registro de investigación biológica sobre el PPB. Los beneficios de realizar investigaciones utilizando estas muestras incluyen la posibilidad de conocer más sobre las causas del PPB y otras enfermedades, la manera de prevenirlas y la manera de tratarlas. Lo que se pudiera aprender podría beneficiar a otras personas en el futuro y probablemente no sea beneficioso para su hijo.

Los participantes de este estudio no recibirán ningún pago por participar ni obtendrán ganancias de ningún producto nuevo que se desarrolle a partir de la investigación realizada con sus muestras.

¿EXISTE ALGÚN RIESGO?
El mayor riesgo para usted o su hijo es la entrega no deseada de la información personal y privada de la historia clínica. Haremos todo lo posible para garantizar que su información personal se mantenga confidencial.

La información se guarda en consultorios cerrados con llave y en computadoras protegidas con contraseña. La probabilidad de que la información personal se entregue a otra persona es muy baja.

¿DÓNDE PUEDO OBTENER MÁS INFORMACIÓN SOBRE ESTA INVESTIGACIÓN DEL MODO EN QUE SE USA EL TEJIDO EN INVESTIGACIONES?
Si tiene preguntas, hable con el médico u otro integrante del personal de soporte de pacientes del hospital donde se atiende su hijo.

Asimismo puede comunicarse con la oficina del coordinador del Registro de tratamiento y aspectos biológicos en Children's Hospitals and Clinics of Minnesota para aclarar sus dudas: Dr. Kris Ann Schultz (612-813-7115 o krisann.schultz@childrensmn.org). También puede llamar al administrador del Comité de Revisión Institucional (IRB) de Children's Hospitals and Clinics of Minnesota al (612) 813-7646 en Minneapolis, Minnesota. EE. UU.

Se adjunta a este formulario de consentimiento un documento llamado “¿Cómo se utiliza el tejido en investigaciones?”. 
SU DECISIÓN SOBRE LA PARTICIPACIÓN EN EL REGISTRO DE ASPECTOS BIOLÓGICOS DEL PPB

Uno de los padres puede autorizar la participación de un niño en la parte 2: el Registro de investigaciones biológicas sobre el PPB. Para que los padres participen, la madre del paciente debe autorizar su propia participación y el padre del paciente debe hacer lo propio. Lea la información a continuación y analice sus opciones. Independientemente de cuál sea su decisión, esta no afectará a la atención del PPB de su hijo.

Una vez que haya leído cada enunciado, marque con un círculo la opción “Sí” o la opción “No”, y coloque su firma y la fecha en los espacios provistos.

Consentimiento para participar en la investigación del Registro de aspectos biológicos sobre el PPB:
- antecedentes médicos familiares, y almacenamiento de tejido tumoral y saliva o sangre para investigaciones

1. La participación de su hijo en el Registro de aspectos biológicos sobre el PPB
Acepto que se obtengan los antecedentes médicos familiares de mi hijo. También acepto permitir la obtención de muestras de saliva o sangre de mi hijo y su almacenamiento, así como de cualquier tejido tumoral del PPB sobrante (si lo hubiera) de mi hijo para usarlo en estudios de investigación relacionados con el PPB.

Sí  No

Firma del padre, de la madre o del tutor  Vínculo con el paciente
Fecha

2. Participación de la MADRE del paciente con PPB en el Registro de aspectos biológicos sobre el PPB
Acepto que se obtengan mis antecedentes médicos familiares. También acepto permitir la obtención de mis muestras de saliva o sangre y su almacenamiento para usarlas en estudios de investigación relacionados con el PPB.

Sí  No

Firma de la MADRE  Fecha

3. Participación del PADRE del paciente con PPB en el Registro de aspectos biológicos sobre el PPB
Acepto que se obtengan mis antecedentes médicos familiares. También acepto permitir la obtención de mis muestras de saliva o sangre y su almacenamiento para usarlas en estudios de investigación relacionados con el PPB.

Sí  No

Firma del PADRE  Fecha

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AUTORIZACIÓN PARA ENTREGAR INFORMACIÓN

Consentimiento para pacientes del Registro internacional de tratamiento y aspectos biológicos sobre el PPB tipo II y III que participan en instituciones diferentes de CHCMN.
REGISTRO INTERNACIONAL DE TRATAMIENTO Y ASPECTOS BIOLÓGICOS SOBRE EL BLASTOMA PLEUROPULMONAR

Nombre del paciente: ______________________________________ Fecha de nacimiento: ______________________________

en letra de imprenta (día / mes / año)

Autorizo a la persona que menciono a continuación a entregar información clínica y de laboratorio sobre mi hijo anteriormente nombrado:

Nombre del médico: ________________________________________________________

Nombre del hospital: ________________________________________________________

Se requiere la siguiente información:

- Resúmenes de alta del hospital.
- Informes de patólogos sobre muestras quirúrgicas, médula ósea, el factor de estimulación de colonias (colony stimulating factor, CSF).
- Informes quirúrgicos.
- Informes radiológicos (radiografía, exploración mediante CT, exploración mediante MRI, exploración ósea, etc.) y/o copias de películas radiográficas, exploraciones, archivos electrónicos.
- Registros de tratamiento (quimioterapia, radioterapia, que incluyen trazados de quimioterapia).
- Consultas.
- Informes CLÍNICOS de oncología pediátrica.
- Muestras patológicas para confirmar el diagnóstico y la inscripción en el Registro del PPB.
- Antecedentes médicos familiares que incluyen un diagrama de los antecedentes médicos.

Envíe la información solicitada a:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, EE. UU.
Correo electrónico: gretchen.williams@childrensmn.org

Entiendo que la información de mi historia clínica (la historia clínica de mi hijo) puede incluir información sobre enfermedades de transmisión sexual, síndrome de inmunodeficiencia adquirida (SIDA) o infección por el virus de la inmunodeficiencia humana (VIH). También puede incluir información sobre servicios de salud mental o conductual, abuso de menores y tratamiento de consumo de alcohol y drogas.

Esta autorización no tiene fecha de vencimiento, pero entiendo que tengo derecho a revocarla en cualquier momento. Entiendo que si cancelo esta autorización, debo hacerlo por escrito en el Registro del PPB. Entiendo que la cancelación de esta autorización no se aplicará a la información que ya ha sido revelada o entregada.

Entiendo que la autorización de la entrega de esta información sobre la salud es voluntaria. Puedo negarme a firmar esta autorización. Entiendo que puedo inspeccionar o copiar la información que se va a usar o entregar. Entiendo que cualquier entrega de información implica la posibilidad de entregarla de nuevo y es posible que la información no esté protegida por las normas federales de privacidad.

<table>
<thead>
<tr>
<th>Nombre del padre, de la madre o del tutor (en letra de imprenta)</th>
<th>Fecha de la firma</th>
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<tr>
<td>Firma del padre, de la madre o del tutor</td>
<td>Relación con el paciente</td>
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<td>Dirección</td>
<td>Ciudad</td>
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<td>Teléfono particular del padre, de la madre o del tutor</td>
<td>Teléfono laboral del padre, de la madre o del tutor</td>
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NOTE: This is the Consent only

No HIPAA, Assent, or attachments translations included
Blastoma pleuropulmonar (PPB) tipo I - Consentimiento informado

Registro internacional de tratamiento y biología del blastoma pleuropulmonar (PPB)

Nombre del participante (en letra de imprenta)

Registro internacional de tratamiento y biología del blastoma pleuropulmonar

Oficina del Registro de tratamiento y biología del PPB (PPB Treatment and Biology Registry Office)
Registro internacional del PPB (International PPB Registry)
Children's Hospitals and Clinics of Minnesota
2525 Chicago Ave S., MS 17-412
Minneapolis, MN 55404, EE. UU.

FORMULARIO DE CONSENTIMIENTO PARA LA INVESTIGACIÓN – PPB tipo I

INTRODUCCIÓN

Se le pide que participe en un estudio de investigación sobre cáncer infantil denominado Registro de tratamiento y biología. Está dirigido a niños que tienen el tumor de pulmón infantil poco común que se denomina blastoma pleuropulmonar (pleuropulmonary blastoma, PPB). Un Registro de tratamiento y biología consiste en la obtención de información clínica y muestras biológicas (tejido tumoral y saliva o sangre) de pacientes con PPB y de su padre y su madre. Para participar, es necesaria su aceptación, pero es su elección. Se le pide que participe porque a su hijo se le diagnosticó PPB tipo I.

□ Si usted es el padre, la madre o el tutor legal de un niño que puede incluirse en este Registro de biología y tratamiento, se requiere su permiso para incluir a su hijo.

□ Si usted es paciente con PPB tipo I y tiene la edad suficiente para dar su consentimiento para participar en el tratamiento sin el permiso de su padre y su madre (más de 17 años de edad en la mayoría de las instituciones), la frase “su hijo” en este formulario de consentimiento se refiere a usted.

□ En función de las prácticas del hospital de su hijo, si tiene la edad suficiente para comprender algunos aspectos de la atención médica (en general, de 7 a 17 años de edad), es posible que se requiera la “aceptación” (el consentimiento) de su hijo, además del consentimiento de uno de los padres.

Este Registro de tratamiento y biología tiene dos partes:

Parte 1: Obtención de datos sobre niños que tienen PPB tipo I (“PPB quístico”) y sobre el tratamiento que reciben. Los niños a quienes se les diagnosticó PPB tipo I recibirán tratamiento de conformidad con las decisiones que se tomen en su propio hospital. Se obtendrá información sobre el tratamiento administrado y sobre la evolución del niño a partir de ese momento.

Parte 2: La segunda parte de este estudio requiere investigar la biología del PPB y las posibles causas genéticas. Esto implica la obtención de información sobre los antecedentes...
médicos familiares y la obtención de muestras del quiste pulmonar (tumor quístico) y muestras de saliva y/o sangre para investigación biológica.

El médico puede explicarle este proyecto de investigación a usted. Usted puede elegir que su hijo participe o no. Su hijo puede participar en la Parte 1 o en la Parte 2, o en ambas. En una investigación como esta, se incluye solo a las personas que eligen participar. Dedique el tiempo que necesite para tomar una decisión sobre la participación. Puede analizar su decisión con amigos, familiares u otros asesores de confianza. También puede analizarla con el equipo de atención médica. Si tiene preguntas, puede pedirle más explicaciones al médico o a los integrantes del personal del Registro.

Un grupo de centros de cáncer infantil de muchos países dirige este Registro de tratamiento y biología. La investigación está coordinada por el Registro internacional de PPB con base en Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota, EE. UU.; Barnes-Jewish and Children's Hospitals of Washington University, St Louis, Missouri, EE. UU.; y Children’s National Medical Center, Washington, D. C., EE. UU.

¿EN QUÉ CONSISTE EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Se le pide que participe en este estudio porque su hijo tiene un tumor maligno (canceroso) poco común que se denomina blastoma pleuropulmonar tipo I (PPB tipo I, también llamado PPB quístico).

1. ¿Qué es el PPB y el PPB tipo I? El PPB es un tumor muy poco común. Aparece en el tejido que se denomina “pleura” (la pleura recubre el interior de la cavidad torácica y también recubre la superficie del pulmón); el PPB también puede aparecer en el tejido “pulmonar”, que constituye el pulmón mismo. En general, el PPB es un tipo de cáncer que se produce en niños pequeños, de menos de 72 meses de edad, pero puede ocurrir en niños mayores. El PPB no está relacionado con los tipos de cáncer de pulmón que se producen en adultos.

Existen tres tipos de PPB: PPB tipos I, II y III. El PPB tipo I consiste en un quiste en el pecho. En las radiografías, los quistes del PPB tipo I se parecen a los quistes pulmonares benignos (no cancerosos) de niños pequeños que se denominan “malformación adenomatoide quística congénita (congenital cystic adenomatoid malformation, CCAM)” o “malformación congénita de la vía aérea pulmonar (congenital pulmonary airway malformation, CPAM)”, que el médico puede explicarle. El PPB tipo I se diagnostica con el microscopio después de extirpar quirúrgicamente un quiste. El PPB tipo I es maligno. Es una enfermedad maligna temprana que en general se cura. Si el PPB tipo I no secura mientras es de tipo I, puede avanzar hasta las formas mucho más graves de PPB que se denominan PPB tipo II y tipo III. No hay casos conocidos de PPB tipo I que se disemine a otras partes del cuerpo.

2. Tratamiento del PPB tipo I: Los niños que tienen PPB tipo I requieren cirugía para extirpar el quiste pulmonar de la manera más completa posible. Después de la cirugía, existen diferentes opiniones sobre si el tratamiento adicional (quimioterapia; terapia con fármacos contra el cáncer) es útil para curar a niños. Algunos oncólogos pediátricos eligen usar quimioterapia para el PPB tipo I; otros eligen no usarla. Los médicos no “saben” qué es lo mejor para el PPB tipo I porque es muy poco común. Nunca se reunió a un grupo grande de niños que tuvieran PPB tipo I a fin de determinar cuáles son los tratamientos que dan mejores resultados.

En este estudio de investigación, se sugiere el uso de cirugía lo más completa posible para el PPB tipo I. Luego, el médico de su hijo decidirá si recomienda quimioterapia. Si, en efecto, el médico de su hijo recomienda la quimioterapia, puede considerar el uso de la pauta de quimioterapia preparada por este Registro de tratamiento y biología, pero no hay información para juzgar si esta pauta es mejor que otro tipo de quimioterapia que su médico pueda elegir.
En este Registro, se obtendrá información sobre cómo se tratan los casos de PPB tipo I. Después de que se hayan obtenido suficientes casos y haya transcurrido tiempo suficiente para obtener información sobre cómo les fue a los niños, los resultados se pondrán a disposición para ayudar a los médicos a obtener información sobre cuáles son las terapias que pueden resultar útiles para el PPB tipo I.

3. Biología y genética del PPB: En el 30% al 40% de los casos, los niños con PPB o los integrantes de su familia tienen otras afecciones médicas. Una de estas afecciones son los quistes pulmonares que pueden convertirse en tipos de cáncer graves. La evolución de los quistes pulmonares en tumores sólidos graves y en ciertas enfermedades se denomina “biología del PPB”. Esto sugiere que una anormalidad genética, como una alteración en el ADN (una mutación), predispone a algunos integrantes de la familia a tener PPB u otras afecciones y puede transmitirse de generación en generación. Se encontró una mutación (anormalidad en el ADN) en algunas familias que tienen PPB, pero es necesario investigar más para comprender cuántos casos de PPB presentan esta mutación y cómo puede causar la enfermedad.

Las enfermedades que se relacionan con el PPB son quistes pulmonares, otros casos de PPB, quistes renales, algunos tipos de cáncer infantiles, algunos tumores en los testículos y los ovarios, pólipos en el intestino delgado y otras varias afecciones muy poco comunes. Se deben realizar investigaciones para determinar una lista completa de afecciones relacionadas con el PPB. No todas estas afecciones constituyen algún tipo de cáncer. La mayoría de los integrantes de las familias con PPB son normales.

¿QUÉ IMPLICA EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Parte 1 del estudio: Obtención de datos sobre el tratamiento del PPB tipo I:
Existen tres maneras principales de tratar el cáncer y el PPB:

- **Cirugía** para extirpar los tumores cancerosos.
- **La quimioterapia** es el uso de fármacos contra el cáncer para detener el crecimiento de las células cancerosas.
- **La radioterapia** es el uso de rayos X de alta energía u otros tipos de radiación para destruir las células cancerosas.

La cirugía es necesaria para el PPB tipo I. Se desconoce si la quimioterapia para el PPB tipo I mejora las probabilidades de curarse. Algunos médicos recomiendan quimioterapia; otros médicos no. El médico y sus colegas decidirán si recomiendan quimioterapia para su hijo. La radioterapia no se usa para el PPB tipo I.

En esta investigación, se obtendrá información sobre cómo se tratan los niños con PPB tipo I y qué resultados se obtienen.

Parte 2 del estudio: Investigación de la biología y la genética del PPB:

Es necesario obtener mucha más información sobre antecedentes médicos familiares, sobre la biología del PPB y sobre los factores genéticos que podrían causar algunos casos de PPB. En este estudio, se pide permiso para obtener información sobre los antecedentes médicos familiares, para guardar partes sobrantes del tumor (quiste) de PPB tipo I del niño, y para obtener y guardar saliva o sangre del niño, de la madre y del padre para fines de investigación.
¿POR QUÉ SE CREA EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Parte 1 del estudio: El PPB tipo I es muy poco común y no se ha establecido una terapia “estándar” o una “mejor” terapia. La cirugía es necesaria. Aparte de eso, no hay información suficiente para saber si la quimioterapia cura a más niños que la cirugía sola. El objetivo de este estudio de investigación es obtener información sobre cómo se trata el PPB tipo I y analizar la información para determinar si el uso de quimioterapia después de la cirugía ayuda a curar a más niños.

Parte 2 del estudio: Se debe obtener mucha información sobre la biología y la genética del PPB y las afecciones médicas relacionadas. En este estudio, se obtienen los antecedentes médicos familiares y se establece la obtención de muestras de pacientes que tienen PPB y de su padre y su madre para investigación a fin de intentar responder algunas de estas preguntas.

En resumen, los objetivos de este Registro de tratamiento y biología son:

1) Obtener datos sobre el tratamiento del PPB tipo I e información sobre los índices de éxito de diferentes tratamientos.

2) Obtener antecedentes médicos familiares, y obtener y guardar muestras de quiste de PPB tipo I y muestras de saliva o sangre del niño con PPB y de su padre y su madre, a fin de obtener más información sobre la biología del PPB y los factores genéticos del PPB.

¿CUÁNTAS PERSONAS PARTICIPARÁN EN EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Calculamos que en este Registro se reunirán aproximadamente 20 a 30 pacientes con PPB tipo I por año procedentes de todo el mundo.

¿QUÉ SUCEDERÁ SI MI HIJO FORMA PARTE DEL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Parte 1 del estudio. Tratamiento del PPB tipo I: Independientemente de que su hijo participe o no en esta investigación, los médicos de su hijo usarán su mejor criterio para evaluar y tratar a su hijo: qué alcance tendrá la cirugía y si se utilizará o no quimioterapia. En esta investigación, se obtendrá información sobre su hijo y sobre cómo se trató el PPB tipo I. Esto incluye, además, la obtención de radiografías y tejido de la cirugía para revisar y confirmar el diagnóstico del PPB tipo I.

Parte 2 del estudio. Biología y genética del PPB: Para los estudios de biología y genética de esta investigación se requieren las siguientes muestras biológicas:

- Del niño con PPB:
  - Después de cumplir todos los requisitos de diagnóstico, guardar parte del tejido tumoral adicional extirpado en la cirugía para estudios de investigación.
  - Obtención de sangre o saliva para muestras de ADN para estudios de investigación.

- De la madre:
  - Obtención de sangre o saliva para muestras de ADN para estudios de investigación.

- Del padre:
  - Obtención de sangre o saliva para muestras de ADN para estudios de investigación.
Además, se obtendrá información sobre los antecedentes médicos familiares. La información adicional sobre la Parte 2 de esta investigación se encuentra más adelante en este formulario de consentimiento.

¿CUÁNTO TIEMPO PARTICIPARÁ MI HIJO EN EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
A su hijo se le realizará un seguimiento indefinido a fin de determinar el desenlace del PPB tipo I.

El tejido del quiste de PPB obtenido al momento de la cirugía inicial se guardará indefinidamente para usarlo para la investigación de las causas y el tratamiento del PPB. Además, se guardarán indefinidamente muestras de sangre o saliva de su hijo y de la madre y el padre para investigar las causas, la biología y el tratamiento del PPB.

¿MI HIJO PUEDE INTERRUMPIR SU PARTICIPACIÓN EN ESTE REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Sí. Usted puede decidir que su hijo interrumpa su participación en este Registro en cualquier momento. Infórmese al Registro de tratamiento y biología y comuníquele al médico de su hijo que quiere retirar su permiso para que participe. La información de contacto se incluye en otras partes de este formulario de consentimiento. El médico de su hijo continuará atendiendo a su hijo independientemente de la decisión de retirarlo de este Registro.

(Si su hijo deja de participar en este estudio, no será posible retirar la información sobre su hijo de los resúmenes de los datos del estudio que ya se hubiesen incorporado en presentaciones o publicaciones científicas. No se incluirá a su hijo en los resúmenes del estudio ni las investigaciones que se realicen en el futuro).

¿CUÁLES SON LOS RIESGOS PARA MI HIJO POR PARTICIPAR EN EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
No hay riesgos médicos específicos para su hijo por estar incluido en este Registro de tratamiento y biología. Su hijo recibirá la misma atención médica de los médicos y el hospital independientemente de que participe o no en este Registro. Existe un leve riesgo de que, debido a que la historia clínica de su hijo se comparte con este Registro, se pueda producir una pérdida de la confidencialidad. Se toman muchas medidas para mantener la confidencialidad de toda la información personal, como se describe más adelante.

¿HAY BENEFICIOS POR PARTICIPAR EN EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
No hay ningún beneficio inmediato o directo por estar incluido en este Registro de tratamiento y biología. De manera indirecta, tener los datos médicos de su hijo en el Registro les ayudará a los médicos y los investigadores a obtener más información sobre el PPB y su tratamiento. La información puede resultar útil para el tratamiento del PPB en el futuro. Además, el estudio de las muestras biológicas de este Registro puede mejorar la comprensión de las causas del PPB y las afecciones médicas relacionadas, cómo detectarlas antes, cómo predecir cuáles son las personas susceptibles de desarrollarlo en las familias y, quizás, cómo tratar el PPB de manera más exitosa.

¿QUÉ OTRAS OPCIONES TENGO SI NO PARTICIPO EN EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Puede elegir participar o no en esta investigación. Este Registro de tratamiento y biología intenta reunir a un grupo grande de pacientes con PPB tipo I para la evaluación de los resultados de su tratamiento y para estudios de la biología y la genética del PPB. No hay ningún otro grupo en el mundo que esté intentando hacer esto por el PPB. Usted dispone de la alternativa de no participar en esta investigación ni en ninguna investigación de este tipo.
Si elige no participar, no tendrá ningún efecto en la atención que su hijo recibirá del médico o el hospital de su hijo.

¿EL MÉDICO Y EL HOSPITAL DE MI HIJO APROBARON EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
Cuando un estudio de investigación de cáncer infantil explica exactamente cómo debe tratarse una enfermedad, se le exige a cada hospital participante que revise y apruebe el estudio antes de que se les pregunte a sus pacientes si participarán o no en el tratamiento de investigación. En este Registro de tratamiento y biología del PPB, no se explica cómo se debe tratar a los niños que tienen PPB (el médico de su hijo y sus colegas toman esas decisiones), por lo que no es obligatorio que este Registro se haya revisado y aprobado en el hospital de su hijo. Aunque tal vez no sea obligatorio, algunos hospitales eligen de hecho revisar formalmente un proyecto como este.

Este proyecto de Registro de tratamiento y biología del PPB se aprobó en los hospitales para niños de Minnesota, Missouri y Washington, D. C. que coordinan la investigación.

Independientemente de que el médico y el hospital de su hijo hayan aprobado específicamente este proyecto de investigación, se requiere su consentimiento para la participación. Muchas instituciones alientan a los padres a considerar la participación en registros como este para enfermedades poco comunes porque es la única manera práctica de obtener información sobre un grupo grande de niños que tienen una enfermedad poco común.

¿SE MANTENDRÁ LA PRIVACIDAD DE LA INFORMACIÓN MÉDICA SOBRE MI HIJO?
Haremos todo lo posible para asegurarnos de que se mantenga la privacidad de la información personal en la historia clínica de su hijo. Las oficinas del Registro de tratamiento y biología (Minnesota, Missouri y Washington, D. C.) mantienen archivos y datos en oficinas bajo llave y en computadoras protegidas por contraseña. Los nombres de los pacientes se reemplazarán en los archivos y los registros informáticos por números de caso del Registro asignados de manera aleatoria. Si la información de este Registro se publica o presenta en reunion científicas, no se utilizará el nombre de su hijo ni ninguna otra información personal. No podemos garantizar la privacidad total, pero las probabilidades de que se entregue la información personal a alguna otra persona son muy pocas.

Las prácticas de privacidad de este Registro de tratamiento y biología se incluyen al final de este formulario de consentimiento.

¿CUÁLES SON LOS COSTOS POR PARTICIPAR EN EL REGISTRO DE TRATAMIENTO Y BIOLOGÍA?
No hay ningún costo por participar en esta investigación. Usted y su hijo no recibirán ningún pago por participar en este Registro de tratamiento y biología.

¿CUÁLES SON MIS DERECHOS SI PARTICIPIO EN ESTE ESTUDIO?
La participación en este Registro de tratamiento y biología es voluntaria. Usted puede elegir que su hijo no participe y puede retirarlo del Registro en cualquier momento. La atención médica que recibirá su hijo en su hospital local será la misma independientemente de que usted decida participar o no en el Registro o de que elija retirarse posteriormente.
¿QUIÉN PUEDE RESPONDER MIS PREGUNTAS SOBRE ESTE REGISTRO?
Puede hablar con el médico local sobre las preguntas o preocupaciones que tenga sobre esta investigación. El médico puede indicarle que consulte a un administrador del Comité de Investigaciones o de Ética local del hospital que también puede ayudarlo. Usted también puede elegir analizar la participación con personal de apoyo del hospital de su hijo, como trabajadores sociales o asesores que brindan apoyo familiar.


CONSENTIMIENTO PARA PARTICIPAR y FIRMAS

Se le pide que dé su consentimiento por separado para las Partes 1 y 2 de este Registro de tratamiento y biología.

Parte 1: Obtención de información sobre el tratamiento del PPB tipo I

He recibido una copia de este formulario de consentimiento. He leído (o me han leído) este formulario. Entiendo la información y he recibido respuestas a mis preguntas.

Acepto que mi hijo participe en la Parte 1: Obtención de información sobre el tratamiento del PPB tipo I del Registro de tratamiento y biología.

NOMBRE DEL PACIENTE ________________________________

Padre, madre o tutor legal ___________________________      __________________________

Nombre (en letra de imprenta)  Firma

Vínculo con el paciente: ____________________  FECHA _____________________
**Responda también esta pregunta:**

A los investigadores que estudian el PPB les gustaría obtener su permiso para poder comunicarse con usted en el futuro si se identifican nuevos temas de investigación relacionados con el PPB para los cuales su participación podría ser útil.

¿Acepta que se comuniquen con usted en el futuro por estudios de investigación especiales adicionales sobre el PPB?  (No es necesario que acepte).

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**SI ACEPTA:**

Nombre:___________________________________________
Dirección:  __________________________________________
___________________________________________
Ciudad, Estado, Código postal:  __________________________________________
Número de teléfono:  __________________________________________
Dirección de correo electrónico:  __________________________________________

N.º del IRB: 0909-082  
Aprobación inicial del IRB: 22/12/2009  
Aprobación más reciente del IRB: 22/07/2015
Parte 2: Obtención y almacenamiento de muestras biológicas para investigación

“INVESTIGACIÓN DE LA BIOLOGÍA” DEL PPB
Esta sección de este formulario de consentimiento abarca estudios de investigación de la biología del PPB y los posibles factores genéticos que pueden ser responsables de algunos casos de PPB. Estas actividades de investigación son independientes de la obtención de datos sobre cómo se trata el PPB tipo I.

Pedimos que el paciente con PPB y la madre y el padre del niño participen en esta investigación. Usted puede participar o negarse a participar en estos estudios adicionales.

(Su hijo puede inscribirse en la Parte 1 para la obtención de información sobre el tratamiento del PPB tipo I, incluso si usted dice que “no” quiere participar en la Parte 2 de investigación de la biología del PPB. Como alternativa, usted y su hijo pueden participar en estudios biológicos sin participar en la Parte 1 sobre el tratamiento del PPB tipo I).

¿QUÉ IMPLICA ESTA INVESTIGACIÓN SOBRE LA BIOLOGÍA DEL PPB?
Le pedimos su permiso para hacer lo siguiente:
6. Obtener los antecedentes médicos de su familia, registrando la información médica sobre sus hijos y familiares de manera de incluir en general a personas de 2 a 4 generaciones de su familia.
7. Guardar el tejido del quiste de PPB que sobre (si está disponible) de la cirugía de su hijo. Se lo guardará en un banco de tejidos, que es un laboratorio en el que se guardan tumores y otras muestras para estudios de investigación.
8. Obtener y guardar muestras de saliva o sangre de su hijo y de cada padre biológico para investigación.

La cantidad de saliva que se obtendrá será de aproximadamente 2 cucharadas (30 ml) y la cantidad de sangre será de alrededor de 2 cucharaditas (10 ml). En la mayoría de los casos, se obtendrá saliva. El tejido del quiste de PPB se obtendrá del quiste extirpado en la cirugía después de cumplir todos los requisitos de diagnosticó.

Las muestras que se guarden en este Registro de biología se utilizarán para obtener muchos detalles sobre las células cancerosas del PPB y las células normales que pudieran rodear a las células cancerosas. Esto incluye observar sustancias químicas y quizás genes (ADN) del interior del tejido y tratar de saber con exactitud en qué se diferencia el cáncer del tejido normal. Se investigará el ADN de la saliva, la sangre o el tejido tumoral a fin de determinar si se puede detectar algún cambio sistemático que pudiera ser parte de la causa del PPB y de las afecciones médicas relacionadas. Los resultados de esta investigación no se incluirán en su historia clínica ni en la de su hijo.

El tejido quístico de su hijo y las muestras de saliva o sangre obtenidas de usted y de su hijo se usarán solo para investigación y no se venderán. Las investigaciones realizadas con estas muestras posiblemente ayuden a desarrollar productos nuevos en el futuro.

Antes de que decida si quiere participar en este Registro de la biología del PPB, aquí se incluye información adicional:

¿POR QUÉ SE REALIZA ESTA INVESTIGACIÓN?
El PPB es un tipo de cáncer infantil poco común porque está relacionado con otras afecciones del paciente o de miembros de la familia en aproximadamente el 40% de los casos. Estos descubrimientos sugieren que en algunos casos de PPB y en algunas familias en las que un niño tiene PPB, un factor
genético predispone a miembros de la familia al PPB y a diversas afecciones relacionadas con el PPB. Es necesario obtener mucha más información sobre los antecedentes médicos familiares y sobre la causa del PPB y la frecuencia con que existe una predisposición familiar. El objetivo de los estudios biológicos es obtener antecedentes familiares y muestras que puedan usarse para investigación de patrones familiares de PPB y enfermedades relacionadas. Los antecedentes y las muestras se guardarán indefinidamente para usos de investigación por parte de los investigadores que tengan ideas aprobadas por un comité de investigación relacionado con este Registro de tratamiento y biología.

La investigación se realizará en diversos laboratorios. Los resultados de estos estudios no afectarán directamente el tratamiento del PPB que recibe su hijo y, en consecuencia, los resultados de las pruebas no formarán parte de la historia clínica de su hijo. En el futuro, las personas que realicen investigaciones con estas muestras posiblemente necesiten obtener más información sobre su salud. Si bien este Registro puede entregarles cierta información sobre su salud o la de su hijo, no les proporcionará el nombre, la dirección, el número de teléfono ni ninguna otra información que les permita a los investigadores saber quién es usted.

Además, es importante que comprenda que por la naturaleza de investigación de estas pruebas, los resultados no estarán disponibles para usted ni para los médicos del estudio.

Puede elegir participar o no participar en esta Investigación de la biología del PPB. Su decisión no afectará a la salud de su hijo ni al tratamiento que recibe.

¿POR CUÁNTO TIEMPO SE GUARDARÁN LAS MUESTRAS PARA LA INVESTIGACIÓN DE LA BIOLOGÍA?
Las muestras de tejido tumoral, saliva o sangre y los antecedentes médicos familiares se guardarán indefinidamente.

¿PODEMOS MI HIJO O YO INTERRUMPIR LA PARTICIPACIÓN EN ESTE REGISTRO DE BIOLOGÍA?
Sí. Puede informarle al Registro de tratamiento y biología y/o al médico de su hijo en cualquier momento que ya no quiere que se utilice el tejido ni los antecedentes médicos en este Registro de la biología del PPB. La información de contacto se incluye en otras partes de este formulario de consentimiento. Si decide que ya no quiere participar en esta investigación, ni sus muestras y antecedentes ni los de su hijo se seguirán utilizando. Si se usaron antes de ese momento y los resultados se incluyeron en resúmenes o publicaciones, no será posible retirar esos datos.

El médico de su hijo continuará atendiendo a su hijo independientemente de la decisión de retirarlo de este Registro.

¿HAY ALGUNA ALTERNATIVA SI NO PARTICIPO EN ESTA INVESTIGACIÓN BIOLÓGICA?
Puede elegir participar o no en esta investigación. En este Registro de tratamiento y biología se intenta reunir a un grupo grande de participantes de una investigación y no hay ningún otro grupo en el mundo que esté intentando hacer esto por el PPB. Es posible que el médico o el hospital de su hijo esté realizando algún tipo de investigación biológica con tumores y lo alentamos a que considere la posibilidad de participar si está disponible y decide hacerlo. Usted dispone de la alternativa de no participar en esta investigación ni en ninguna investigación de este tipo.
¿EXISTE ALGÚN BENEFICIO?
No hay ningún beneficio directo para usted o su hijo por participar en el Registro de investigación de la biología del PPB. Los beneficios de realizar investigaciones con estas muestras incluyen la posibilidad de obtener más información sobre las causas del PPB y otras enfermedades, y cómo prevenirlas y tratarlas. La información que se podría obtener puede beneficiar a otras personas en el futuro y no es probable que beneficie a su hijo.

Los participantes de este estudio no recibirán ningún pago por participar ni obtendrán ningún beneficio económico por ningún producto nuevo que se desarrolle a partir de la investigación realizada con las muestras.

¿EXISTEN RIESGOS?
El mayor riesgo para usted o su hijo es la entrega accidental de información personal privada de su historia clínica. Haremos todo lo que esté a nuestro alcance para garantizar que se mantenga la confidencialidad de su información personal. La información se mantiene en oficinas bajo llave y en computadoras protegidas por contraseña. Las probabilidades de que la información personal se entregue a alguna otra persona son muy pocas.

¿DÓNDE PUEDO OBTENER MÁS INFORMACIÓN SOBRE ESTA INVESTIGACIÓN O SOBRE LA MANERA EN QUE SE USA EL TEJIDO PARA INVESTIGACIÓN?
Si tiene preguntas, hable con el médico u otro integrante del personal de apoyo a los pacientes del hospital de su hijo.

Además, si tiene preguntas, puede comunicarse con la oficina que coordina el Registro de tratamiento y biología en Children’s Hospitals and Clinics of Minnesota: Dr. Kris Ann Schultz (612-813-7115 o krisann.schultz@childrensmn.org). Puede llamar también al Administrador del Comité de Revisión Institucional de Children’s Hospitals and Clinics of Minnesota al (612) 813-7646 en Minneapolis, Minnesota, EE. UU.

Con este formulario de consentimiento, se incluye un documento titulado “¿Cómo se usa el tejido para investigación?”.

CÓMO TOMAR SU DECISIÓN DE PARTICIPAR EN EL REGISTRO DE LA BIOLOGÍA DEL PPB
Uno de los padres puede autorizar la participación de un niño en la Parte 2: el Registro de la investigación de la biología del PPB. Para que participe el padre o la madre, la madre del paciente debe autorizar su propia participación y el padre del paciente debe autorizar su propia participación. Lea la siguiente información y piense en las opciones que tiene. Independientemente de lo que decida hacer, la atención que recibe su hijo por el PPB no se verá afectada.

Una vez que haya leído cada oración, encierre con un círculo “Sí” o “No” y firme y escriba la fecha en los espacios correspondientes.
Consentimiento para la participación en la investigación del Registro de la biología del PPB:
antecedentes médicos familiares y conservación de tejido quístico y saliva o sangre
para investigación

1. Participación de su hijo en el Registro de la biología del PPB
Acepto permitir que se obtengan los antecedentes médicos familiares de mi hijo. Además, acepto permitir que se obtengan y guarden muestras de saliva o sangre de mi hijo, y permitir que se guarde el tejido del quiste de PPB de mi hijo que sobre (si está disponible) para estudios de investigación relacionados con el PPB.

Sí   No   ____________________________   _____________________
Firma del padre, de la madre o del tutor  Vínculo con el paciente
Fecha

2. Participación de la MADRE del paciente con PPB en el Registro de la biología del PPB
Acepto permitir que se obtengan mis antecedentes médicos familiares. Además, acepto permitir que se obtengan y guarden mis muestras de saliva o sangre para estudios de investigación relacionados con el PPB.

Sí   No   __________________________________
Firma de la MADRE          Fecha

3. Participación del PADRE del paciente que tiene PPB en el Registro de la biología del PPB
Acepto permitir que se obtengan mis antecedentes médicos familiares. Además, acepto permitir que se obtengan y guarden mis muestras de saliva o sangre para estudios de investigación relacionados con el PPB.

Sí   No   __________________________________
Firma del PADRE         Fecha

N.º del IRB: 0909-082   Aprobación inicial del IRB: 22/12/2009
Aprobación más reciente del IRB: 22/07/2015
APPENDIX V: CHILDREN’S HOSPITALS AND CLINICS OF MINNESOTA CONSENTING DOCUMENTS, TYPES I, II, AND III
Appendix V – A: **Type I PPB** Children’s Hospitals and Clinics of Minnesota Consenting Documents
**Type I PPB Informed Consent**

Name of Participant (please print)

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**International Pleuropulmonary Blastoma Treatment and Biology Registry**

Children's Hospitals and Clinics of Minnesota

2525 Chicago Avenue South, Minneapolis, MN 55404

**RESEARCH CONSENT FORM – Type I PPB**

**INTRODUCTION**

You are being asked to participate in a childhood cancer research study called a Treatment and Biology Registry; it is for children with the rare childhood lung tumor called pleuropulmonary blastoma (PPB). A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue) from patients with PPB. To participate, your agreement is necessary, but it is your choice. You are being asked to participate because your child has been diagnosed with Type I PPB.

- If you are a parent or legal guardian of a child who may be included in this Treatment and Biology Registry, your permission is required for your child to be included.

- If you are a Type I PPB patient and are old enough to consent to treatment without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.

- Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (usually ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

- **Part 1:** Collecting data on children with Type I PPB (“cystic PPB”) and on their treatment. Children diagnosed with Type I PPB will be treated according to decisions at their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

- **Part 2:** The second part of this study involves research into the biology of PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens of the lung cyst (cystic tumor) for biological research.

Your doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your health care team. If you have any questions, you can ask your doctor or members of the Registry staff for more explanation.

This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from many countries. The research is coordinated by The International PPB Registry based at Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and
WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?

You are being asked to take part in this study because your child has a rare malignant (cancerous) tumor called Type I pleuropulmonary blastoma (Type I PPB, also called cystic PPB).

1. What is PPB and Type I PPB? PPB is a very rare tumor. It arises in tissue called “pleura” (pleura covers the inside of the chest cavity and also covers the surface of the lung); PPB can also arise in the “pulmonary” tissue, which is the lung itself. PPB is usually a cancer of young children, under age 72 months, but it may occur in older children. PPB is not related to the lung cancers which occur in adults.

There are three types of PPB: Types I, II, and III PPB. Type I PPB is a cyst in the chest. On x-rays, the cysts of Type I PPB look like benign (non-cancerous) lung cysts of young children called “CCAM” or “CPAM”, which your doctor can explain to you. Type I PPB is diagnosed under the microscope after a cyst is surgically removed. Type I PPB is malignant; it is an early malignancy which is usually cured. If Type I PPB is not cured while it is Type I, it can progress to the much more serious forms of PPB called Type II and Type III PPB. There are no known instances of Type I PPB spreading to other parts of the body.

2. Treatment of Type I PPB: Children with Type I PPB require surgery to remove the lung cyst as completely as possible. After surgery, there are different opinions about whether more treatment (chemotherapy; anti-cancer drug therapy) is useful to cure children. Some pediatric cancer doctors choose to use chemotherapy for Type I PPB; some choose not to use it. The reason doctors do not “know” what is best for Type I PPB is that it is so rare. No large group of children with Type I PPB has ever been collected together to determine what treatments work best.

This research study suggests surgery as complete as possible for Type I PPB. Then your child’s doctor will decide whether to recommend chemotherapy. If your child’s doctor does recommend chemotherapy, he or she may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

This Registry will collect information about how Type I PPB cases are treated. After enough cases have been collected and enough time has passed to learn how the children have done, the results will be made available to help doctors learn what therapies may be helpful for Type I PPB.

3. PPB Biology and Genetics: In 30–40% of cases, children with PPB or their family members have other medical conditions. One of these conditions is lung cysts which may develop into serious cancers. The evolution of lung cysts into serious solid tumors and to certain illnesses is called the “biology of PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes some family members to PPB or other conditions and may be passed from generation to generation. A mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB cases have this mutation and how it may cause the disease.

The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.
Study Part 1: Collection of Data on Treatment of Type I PPB:
There are three major ways to treat cancer and PPB:

- **Surgery** to remove cancer tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells.
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells.

Surgery is necessary for Type I PPB. It is not known whether chemotherapy for Type I PPB improves the chance for cure; some doctors recommend chemotherapy; other doctors do not. Your doctor and his or her colleagues will decide whether to recommend chemotherapy for your child. Radiation therapy is not used for Type I PPB.

This research will collect information on how children with Type I PPB are treated and what is their outcome.

Study Part 2: Research into PPB Biology and Genetics:

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB. This study asks for permission to collect family medical history information, to store excess portions of the child’s Type I PPB tumor (cyst).

**WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?**

Study Part 1: Type I PPB is very rare and there is no established “standard” or “best” therapy. Surgery is necessary. After that, there is not enough information to know whether chemotherapy cures more children than surgery alone would do. The goal of this research study is to collect information on how Type I PPB is treated and analyze the information to see whether the use of chemotherapy after surgery helps cure more children.

Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

In summary, the goals of this Treatment and Biology Registry are:

1) To collect data on treatment of Type I PPB and to learn the success rates of different treatments.

2) To collect family medical histories and to collect and save Type I PPB cyst samples from the PPB child in order to learn more about the biology of PPB and genetic factors in PPB.

**HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?**

We estimate that about 20-30 Type I PPB patients per year from around the world will be collected in this Registry.

**WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?**

Study Part 1. Treatment of Type I PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: how much surgery and whether to use chemotherapy. This research will collect information about your child and how the Type I PPB
was treated. This also involves collecting x-rays and tissue from surgery to review and confirm the diagnosis of Type I PPB.

Study Part 2. Biology and Genetics of PPB: The biology and genetic studies of this research involve the following biological samples:

- From the child with PPB:
  - After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies.

In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.

**HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?**
Your child will be followed indefinitely in order to determine the outcome of the Type I PPB.

PPB cyst tissue from the time of initial surgery will be saved indefinitely to be used for research into causes and treatment of PPB.

**CAN MY CHILD STOP BEING IN THIS TREATMENT AND BIOLOGY REGISTRY?**
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)

**WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?**
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

**ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?**
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child's medical data in the Registry will help physicians and researchers learn more about PPB and its treatment. The information may be helpful in the treatment of PPB in the future. Also, study of biologic specimens in this Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat PPB more successfully.

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?**
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of Type I PPB patients for evaluation of the results of their treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or Children’s Hospitals and Clinics of Minnesota.

HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?
When a childhood cancer research study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with PPB are to be treated (your child’s doctor and his or her colleagues make those decisions).

This PPB Treatment and Biology Registry project has been approved at Children’s Hospitals and Clinics of Minnesota and at the children’s hospitals in Missouri and Washington, D.C. who are coordinating the research.

Your consent to participate is required. Many institutions encourage parents to consider participation in Registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.

The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.

WHAT ARE THE COSTS OF TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?
There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?
Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at Children’s Hospitals and Clinics of Minnesota will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS REGISTRY?
For questions about the Registry, contact Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org).
You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (612) 813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES

You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

Part 1: Collection of Information on Type I PPB Treatment

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I agree to have my child be a part of the Treatment and Biology Registry Part 1: Collection of Information on Type I PPB Treatment.

PATIENT'S NAME ________________________________

Parent/legal guardian  _________________________  ___________________________

Print name               Signature

Relationship to patient: __________________  DATE _____________________

Please also answer this question:
Researchers studying PPB would like your permission to be able to contact you in the future if new PPB research topics are identified for which your participation would be helpful.

Do you agree to be contacted in the future about additional, special PPB research studies?   (You do not need to agree to this.)

_____ I agree to be contacted in the future    _____ I do not agree to be contacted in the future

IF YOU AGREE:

Name: ________________________________________

Address: ________________________________________

City, State, Postal/Zip Code: __________________________

Telephone Number: __________________________

Email address: ______________________________________

Physician/Researcher obtaining consent                             Date
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB and possible genetic factors which may be responsible for some cases of PPB. These research activities are separate from collecting data on how Type I PPB is treated.

We ask that the PPB patient and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the collection of Type I PPB Treatment, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in biology studies without taking part in Part 1 on Type I PPB Treatment.)

WHAT DOES THIS PPB BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:

1. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.
2. To save leftover PPB cyst tissue (if available) from your child’s surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies.

Specimens saved in this Biology Registry will be used to learn many details about PPB cancer cells and any normal cells that might surround the cancer cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how the cancer is different from normal tissue. DNA from tumor tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s cyst tissue will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for research into familial patterns of PPB and related diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this Treatment and Biology Registry.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not
give them your name, address, phone number, or any other information that will let the researchers know who you are.

Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

**HOW LONG WILL SPECIMENS BE SAVED FOR BIOLOGY RESEARCH?**
Tumor tissue, and family medical histories will be saved indefinitely.

**CAN MY CHILD OR I STOP BEING PART OF THIS BIOLOGY REGISTRY?**
Yes. You can inform the Treatment and Biology Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

**ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS BIOLOGY RESEARCH?**
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB. It is possible that your child’s doctor or Children’s Hospitals and Clinics of Minnesota is doing some biology research on tumors and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

**ARE THERE ANY BENEFITS?**
There is no direct benefit to you or your child from participating in the PPB Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.

**ARE THERE ANY RISKS?**
The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private. Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.
WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?

If you have any questions, please talk to your doctor or other patient support personnel at Children’s Hospitals and Clinics of Minnesota.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org) You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (612) 813-7646 in Minneapolis, Minnesota USA.

A document called "How is Tissue Used for Research?" is attached to this consent form.

MAKING YOUR CHOICE ABOUT PARTICIPATING IN PPB BIOLOGY REGISTRY

One parent can authorize participation of a child in Part 2: the PPB Biology Research Registry. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s PPB care.

After reading each sentence, circle "Yes" or "No" and write your signature and date in the spaces provided.

Consent for Participation in PPB Biology Registry Research:
Family Medical History and Saving Cyst Tissue for Research

1. Your Child’s Participation in PPB Biology Registry
I agree to allow my child’s family medical history to be collected. I also agree to allow any leftover PPB cyst tissue (if available) from my child to be saved for research studies related to PPB.

Yes  No

Signature of parent/guardian  relationship to patient

Date

Physician/Researcher obtaining consent

Date

IRB# 0909-082  Initial IRB Approval: 12/22/2009
Current IRB approval: 07/22/2015
Type I PPB Informed Assent

Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue South, Minneapolis, MN 55404

Assent Form for Child or Adolescent Ages 7-17 with Type I PPB

We are asking you to take part in a research study because you have pleuropulmonary blastoma (PPB). PPB is a rare type of cancer in the lung. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about PPB and how to treat it. We will do this by collecting records on how doctors treat children with Type I PPB. Based on past experiences, the Registry makes suggestions on how PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want to include you as well. Children and teens with Type I PPB who are part of this study may be treated with surgery and chemotherapy. Your doctor will decide whether to recommend this to your parents and will discuss it with them and you. Chemotherapy is a type of strong medicine that destroys cancer cells. Chemotherapy can also cause side effects that could make you temporarily feel sicker.

As part of a Registry, information about your illness and your surgery and other possible treatments is sent to the main PPB Study research office. Doctors from around the world want to share information about treating children and teenagers who have Type I PPB. By sharing information, we can more quickly learn the best ways to treat cancer. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also send a sample of the cyst that was removed from your chest so that they can learn in the future about how and perhaps why PPB cancers exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it.

Your mother or father or guardian can help you decide whether to agree to this scientific study. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.
Please answer the following questions by circling either YES or NO and entering your initials.

1. My tissue may be sent to the PPB Study office to be used in research about PPB.
   YES  NO  Initials _______

2. My leftover tissue may be kept by the PPB Study office for use in future research studies.
   YES  NO  Initials _______

3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.
   YES  NO  Initials _______

I agree to take part in this study.

Assent by child/adolescent  

To the professional:
If the child does not sign the form but you believe the child has actively assented, please document on this form. State the specific behaviors (child shook head yes, child said “OK” after I described procedure, etc.).

Physician/Researcher obtaining consent  

IRB# 0909-082  
Initial IRB Approval: 12/22/2009
Current IRB approval: 07/22/2015
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________

Please print ____________________________ (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________

Hospital Name: ____________________________________________________

The following information is requested:

- Hospital discharge summaries
- Pathologist’s reports on surgical specimens, bone marrow, CSF
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
- Treatment records (chemotherapy, radiation therapy, including chemo roadmaps)
- Consultations
- Pediatric Oncology CLINIC records
- Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
- Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.
Telephone: 612 813 7115
Fax: 612 813 7108
E-mail: gretchen.williams@childrensmin.org

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

____________________________________________    _____________________________
Printed Name of Parent or Guardian      Date Signed

____________________________________________    _____________________________
Signature of Parent or Guardian      Relationship to Patient

Address             City       State          Zip Code

_____________________________________     _____________________________
Parent or Guardian Home Phone      Parent or Guardian Work Phone
Types I, II & III PPB HIPAA Authorization Form

________________________________
Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue South, Minneapolis, MN 55404

Health Insurance Portability and Accountability Act (HIPAA)
Authorization to Use/Disclose Protected Health Information for Research

International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects you and your child’s individually identifiable health information (protected health information). The privacy law requires you or your child to sign an authorization in order for researchers to be allowed to use or disclose your/your child’s protected health information for research purposes in the study entitled International PPB Treatment Study.

What protected health information may be used or disclosed?

Your/your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, tumor measurement, x-rays and scans, and pathology results
- Results of tests to monitor for side effects including hearing tests, heart tests, lung tests, learning ability
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

What will your or your child's protected health information be used for?

The main reason to use your or your child’s health information is to be able to conduct research into PPB treatments and into scientific, biologic research on PPB. PPB is a very rare malignant disease in the lung of young children. It occurs in three forms: Types I, II, and III PPB. Because it is so rare, consistent treatment of a large group of children has never occurred, and treatment success is therefore very difficult to judge. In addition, PPB appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment Study has three purposes:

1. For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease.
treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

2. For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

3. To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on PPB children and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store PPB tissue.

In addition to these PPB research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

Who may disclose your/your child’s protected health information to the researchers?

If you agree to your child’s participation in this PPB study, the study researchers and their staff may obtain your or your child’s protected individual health information from Children’s Hospitals and Clinics of Minnesota.

With whom would the protected health information be shared?

Your/your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child's hospital who not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital
What is the potential for re-disclosure of your/your child’s protected health information?

All reasonable efforts will be used to protect the confidentiality of your or your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your or your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your or your child’s confidentiality will be compromised.

What happens if I do not sign this permission form?

If you do not sign this permission form, your child will not be a part in this PPB research study for which your child is being considered.

For how long will you/your child’s protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

What are your or your child’s rights after signing this Authorization form?

You/your child have the right to withdraw from participating in this research. You have the right to revoke in writing your permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your permission to conduct the research and related activities such as oversight. Even if you revoke your permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If you wish to withdraw your permission, contact the investigator and you will be asked to complete a written form.

You have the right to choose not to sign this form. If you decide not to sign, your child will not participate in this PPB research. Refusing to sign will not affect the current or future care you/your child receives at your treatment institution and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you/your child choose to share private health information with anyone not directly related to this research, the federal law designed to protect your privacy may no longer protect the shared information.

What are you/your child’s rights to access your/your child’s protected health information?

Subject to certain legal limitations, you have the right to access your child’s protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. You may access this information only after the study analyses are complete. To request this information, you will need to contact your child's doctor or the Institutional Review Board at Children’s Hospitals and Clinics of Minnesota. Findings from future research using material stored in the tissue bank established in this study (PPB tissue from your child) will not be available to you.
By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this PPB study to use and disclose your/your child’s protected health information for the purposes described above. You also permit you/your child’s doctors and other health care providers to disclose you/your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at Children’s Hospitals and Clinics of Minnesota.

**CERTIFICATIONS AND SIGNATURE SECTION**

_I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed._

Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject) OR Research Subject’s Authorized Representative (such as Parent or Guardian)  
Date

Printed name of Research Subject’s Authorized Representative  
Representative’s relationship to Research Subject (for example: “mother” or “father” or “guardian”)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):

IRB# 0909-082  
Initial IRB Approval: 12/22/2009  
Current IRB approval: 07/22/2015
TAKING PART IN GENETIC RESEARCH: ISSUES TO CONSIDER

You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

Considering Possible Benefits
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

Considering Possible Risks
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child's point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

Insurance Coverage
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

Employment or Other Qualification Decisions
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

Emotional Effects of Genetic Information
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
• what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
• if the researcher will keep other information with the sample
• if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
• What is the purpose of the study?
• What is my doctor’s involvement in the study?
• Who is paying for the study?
• Will I be able to get the information from the genetic testing?
• Will anyone else get the information from the genetic testing?
• Will the information from the study help me or my child?
• Will the information from the study help other people with this disease or condition?
• How are the costs of the study being paid, and will my insurance company be billed?
• Will the information be in my or my child’s medical record?
• What will happen to the sample after the study is done, and do I have any control of that?
• Will any other information be kept with the sample?
• Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child’s physician if you have questions or concerns. You may also contact Children’s Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child’s care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
HOW IS TISSUE USED FOR RESEARCH? WHAT YOU NEED TO KNOW

You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer's. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your gender and age
Your racial or ethnic group
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
Treatment you have received
Your family history
Your medical history

**How is my privacy protected?**
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

**What are the risks to me if I give my tissue to research?**
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

**Can I change my mind?**
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

**What if I have more questions?**
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
Notice of Privacy Practices

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry’s legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to “you” or “your” in this Notice, we refer to the patient. When we refer to types of disclosures of information to “you,” we mean disclosures to the patient, the patient’s guardian, or the person legally authorized to receive information about the patient.

**Your Privacy Rights**

Confidential Communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke Your Written Permission (Authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment and Biology Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

**Use and Disclosure of Your Medical Information**

This Treatment and Biology Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

**Other Uses and Disclosures**

Research: This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information
will be given to someone else is very small. In some cases, where there is only a minimal risk to your privacy (for example, a research project comparing the treatment and outcome of all patients who received chemotherapy for PPB) we may disclose information about you without your written authorization. We will only disclose information about you for research without your authorization when the approval process determines that there is only a minimal risk to your privacy, and we have initiated steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your child's PPB treatment, and therefore the results of the tests will not become part of your child's health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Correspondence: If you have indicated on the consent form that yes, you will allow the PPB Treatment and Biology Registry to contact you with information about new studies or other Registry services that may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this contact could be by leaving messages on a home answering machine or voice mail, by email or by the Postal Service.

Other uses and disclosures: Disclosures of health information not covered by this Notice or the laws that apply to PPB Treatment and Biology Registry will be made only with your written permission.

FOR MORE INFORMATION
If you want more information about your privacy rights, are concerned that the PPB Treatment and Biology Registry has violated your privacy rights, or you disagree with a decision that we made about access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue South
Minneapolis, MN 55404
(612) 813-7115
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children's and you will not be retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights
U.S. Department of Health and Human Services
233 North Michigan Avenue, Suite 240
Chicago, IL 60601
(312) 886-2359 or 1-800-368-1019
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes will apply to information we already have about you and information we receive about you in the future. We will provide an updated Notice to you when you request one. We will also post the most current Notice in public areas and on the PPB Treatment and Biology Registry Children's Web site at www.ppbregistry.org

The effective date of this Notice is May 8, 2009
Appendix V – B:  Types II and III PPB Children’s Hospitals and Clinics of Minnesota Consenting Documents
Types II and III PPB Informed Consent

Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue South, Minneapolis, MN 55404

RESEARCH CONSENT FORM – Types II and III PPB

INTRODUCTION
You are being asked to participate in a childhood cancer research study called a Treatment and Biology Registry; it is for children with the rare childhood lung tumor called pleuropulmonary blastoma (PPB). A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue) from patients with PPB. To participate, your agreement is necessary, but it is your choice. You are being asked to participate because your child has been diagnosed with Type II or Type III PPB.

- If you are a parent or legal guardian of a child who may be included in this research study, your permission is required for your child to be included.
- If you are the PPB patient and are old enough to consent to treatment without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.
- Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (generally, children ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

Part 1: Collecting data on children with Types II and III PPB and on their treatment. Children diagnosed with Types II or III PPB will be treated according to decisions at their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

Part 2: The second part of this study involves research into the biology of PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens of the tumor for biological research.

Your doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your health care team. If you have any questions, you can ask your doctor or members of the Registry staff for more explanation.

This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from many countries. The research is coordinated by The International PPB Registry based at Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and
WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?

You are being asked to take part in this study because your child has a rare malignant (cancerous) tumor called pleuropulmonary blastoma (PPB).

1. **What is PPB and What are Types II and III PPB?** PPB is a very rare tumor. It arises in tissue called “pleura” (pleura covers the inside of the chest cavity and also covers the surface of the lung); PPB can also arise in the “pulmonary” tissue, which is the lung itself. PPB is usually a cancer of young children, under age 72 months, but it may occur in older children. PPB is not related to the lung cancers which occur in adults.

   There are three forms of PPB called Types I, II, and III PPB. Types II and III PPB are quite serious forms of childhood cancer. Types II and III PPB can spread to other parts of the body and special x-ray tests (imaging studies) are used to evaluate this.

2. **Treatment of Types II and III PPB:** Children with Types II and III PPB require surgery, chemotherapy and perhaps radiation therapy for treatment. It is not known what chemotherapy drugs and schedule of drugs are the best for Types II and III PPB. The reason for this is that PPB is very rare. No large group of children with Types II or III PPB has ever been collected together to determine what treatments work best.

   This research study suggests surgery as complete as possible for Types II and III PPB. Sometimes surgery to remove the tumor is not done until chemotherapy has been used to shrink the tumor. Your child’s doctor will decide what chemotherapy drugs and schedule to recommend for treatment of your child. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

   This Registry will collect information about how children with Types II and III PPB cases are treated. After enough cases have been collected and enough time has passed to learn how the children have done, the results will be made available to help doctors learn what therapies may be helpful for Types II and III PPB.

3. **PPB Biology and Genetics:** In 30-40% of cases, children with PPB or their family members have other medical conditions. One of these conditions is lung cysts which may develop into serious cancers. The evolution of lung cysts into serious solid tumors and the familial predisposition to certain illnesses is called the “biology of PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes some family members to PPB or other conditions and may be passed from generation to generation. A mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB cases have this mutation and how it may cause the disease.

   The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.

WHAT DOES THE TREATMENT AND BIOLOGY REGISTRY INVOLVE?
Study Part 1: Collection of Data on Treatment of Types II and III PPB:
There are three major ways to treat cancer and PPB:

- **Surgery** to remove cancer tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells.
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells.

Types II and III PPB tumors often affect large areas of the lung and chest cavity; these PPBs cannot be removed totally by surgery. Standard (usual) treatment around the world for children with Types II and III PPB is surgery and chemotherapy, and sometimes radiation therapy. Instead of major surgery, large tumors are sometimes sampled (biopsied) first; then chemotherapy is used to shrink the tumor; then surgery is used to try to remove remaining tumor. For chemotherapy, there are many different anti-cancer drugs and many possible combinations of these drugs. Around the world, there is no standard combination or standard schedule of anti-cancer drugs for treatment of Types II and III PPB.

Children in this study will have surgery to try to remove the PPB (or a biopsy for diagnosis first with surgery later). Then your child’s doctor and his or her colleagues will decide what chemotherapy drugs and schedule to use. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose. Your child’s doctors will also decide how much surgery should be recommended to remove the PPB tumor and whether radiation therapy should be used.

This research will collect information on how children with Types II and III PPB are treated and what is their outcome.

Study Part 2: Research into PPB Biology and Genetics:

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB. This study asks for permission to collect family medical history information, to store excess portions of the child’s Type II or III PPB tumor.

**WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?**

Study Part 1: Types II and III PPB are very rare and there is no established “standard” or “best” therapy. Around the world, children with PPB have been treated according to decisions made case-by-case over many years in many different hospitals by many different physicians. No treatment has been tested in a large group of Types II and III PPB patients. The goal of this research study is to collect treatment information for Type II and III PPB children and to try to learn how well certain treatments work. Future treatments can be compared to this treatment in order to measure improvements.

Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

In summary, the goals of this Treatment and Biology Registry are:

1) To collect data on treatment of children with Types II and III PPB and to learn the success rates of different treatments.
2) To collect family medical histories and to collect and save Types II and III PPB tumor samples from the PPB child and from the mother and father in order to learn more about the biology of PPB and genetic factors in PPB.

HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
We estimate that about 20-40 Type II or III PPB patients per year will be collected in this Registry.

WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?
Study Part 1. Treatment of Types II and III PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: how much surgery and what chemotherapy medications and schedule to use, and whether to recommend radiation therapy. Your child’s doctor may consider using a chemotherapy guideline prepared by this Treatment and Biology Registry, but there is no information to judge whether this guideline is better than other chemotherapy your doctor may choose.

This research will collect information about your child and on how the Type II or III PPB was treated. This project also involves collecting x-rays and tissue from surgery to review and confirm the diagnosis of Type II or III PPB.

Study Part 2. Biology and Genetics of PPB: The biology and genetic studies of this research involve the following biological samples:

After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies.

In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.

HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?
Your child will be followed indefinitely in order to determine the outcome of the Type II or III PPB.

PPB tumor tissue from the time of initial or subsequent biopsy or surgery will be saved indefinitely to be used for research into causes and treatment of PPB.

CAN MY CHILD STOP BEING IN THIS STUDY?
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)

WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

**ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?**
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child's medical data in the Registry will help physicians and researchers learn more about PPB and its treatment. The information may be helpful in the treatment of PPB in the future. Also, study of biologic specimens in this Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat PPB more successfully.

**WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?**
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of Types II and III PPB patients for evaluation of the results of their treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or Children’s Hospitals and Clinics of Minnesota.

**HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?**
When a childhood cancer research study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with PPB are to be treated (your child’s doctor and his or her colleagues make those decisions).

This PPB Treatment and Biology Registry project has been approved at Children’s Hospitals and Clinics of Minnesota and the children’s hospitals in Missouri and Washington, D.C. who are coordinating the research.

Regardless of whether your child’s doctor and hospital have specifically approved this research project, your consent to participate is required. Many institutions encourage parents to consider participation in Registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

**WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?**
We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.
The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.

**WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?**
There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

**WHAT ARE MY RIGHTS IF I TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?**
Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at Children’s Hospitals and Clinics of Minnesota will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.

**WHO CAN ANSWER MY QUESTIONS ABOUT THIS REGISTRY?**
For questions about the Registry, contact Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org). You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (621) 813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES
You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

Part 1: Collection of Information on Type II and III PPB Treatment

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I agree to have my child be a part of the Treatment and Biology Registry. Part 1: Collection of Information on Types II and III PPB Treatment.

PATIENT’S NAME ____________________________
Printed

Parent/legal guardian ____________________________
Print name __________________ Signature

Relationship to patient: __________________ DATE __________________

Please also answer this question:
Researchers studying PPB would like your permission to be able to contact you in the future if new PPB research topics are identified for which your participation would be helpful.

Do you agree to be contacted in the future about additional, special PPB research studies?

YOU DO NOT NEED TO AGREE TO THIS.

_____ I agree to be contacted in the future _____ I do not agree to be contacted in the future

IF YOU AGREE:
Name: ____________________________
Address: ____________________________
City, State, Postal/Zip Code: ____________________________
Telephone Number: ____________________________
Email address: ____________________________

Physician/Researcher obtaining consent ____________________________ Date ____________________________

IRB# 0909-082 Initial IRB Approval: 12/22/2009
Current IRB approval: 07/22/2015
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB and possible genetic factors which may be responsible for some cases of PPB. These research activities are separate from collecting data on how Types II and III PPB are treated.

We ask that the PPB patient and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the collection of Types II and III PPB Treatment, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in these studies without taking part in Part 1 on Types II and III PPB Treatment.)

WHAT DOES THIS PPB BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:
1. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.
2. To save leftover PPB tumor tissue (if available) from your child’s biopsy and/or surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies.

Specimens saved in this Biology Registry will be used to learn many details about PPB cancer cells and any normal cells that might surround the cancer cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how the cancer is different from normal tissue. DNA from tumor tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s tumor tissue will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for research into familial patterns of PPB and related diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this Treatment and Biology Registry.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not
give them your name, address, phone number, or any other information that will let the researchers know who you are.

Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

**HOW LONG WILL SPECIMENS BE SAVED FOR BIOLOGY RESEARCH?**
Tumor tissue and family medical histories will be saved indefinitely.

**CAN MY CHILD OR I STOP BEING PART OF THIS BIOLOGY REGISTRY?**
Yes. You can inform the Treatment and Biology Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

**ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS BIOLOGY RESEARCH?**
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB. It is possible that your child’s doctor or Children’s Hospitals and Clinics of Minnesota is doing some biology research on tumors and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

**ARE THERE ANY BENEFITS?**
There is no direct benefit to you or your child from participating in the PPB Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.
ARE THERE ANY RISKS?
The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private. Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.

WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?
If you have any questions, please talk to your doctor or other patient support personnel at Children’s Hospitals and Clinics of Minnesota.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz (612-813-7115 or krisann.schultz@childrensmn.org).

You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at (612) 813-7646 in Minneapolis, Minnesota USA.

A document called "How is Tissue Used for Research?" is attached to this consent form.

MAKING YOUR CHOICE ABOUT PARTICIPATING IN PPB BIOLOGY REGISTRY
One parent can authorize participation of a child in Part 2: the PPB Biology Research Registry. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s PPB care.

After reading each sentence, circle "Yes" or "No" and write your signature and date in the spaces provided.
Consent for Participation in PPB Biology Registry Research:
Family Medical History and Saving Tumor Tissue for Research

1. Your Child’s Participation in PPB Biology Registry

I agree to allow my child’s family medical history to be collected. I also agree to allow any leftover PPB
tumor tissue (if available) from my child to be saved for research studies related to PPB.

Yes  No  _________________________  __________________
Signature of parent/guardian  relationship to patient

____________________  
Date

_________________________________________________________________________  
Physician/Researcher obtaining consent  Date

IRB# 0909-082  Initial IRB Approval: 12/22/2009
Current IRB approval: 07/22/2015
Types II & III PPB Informed Assent

Name of Participant (please print)

International Pleuropulmonary Blastoma Treatment and Biology Registry
Children's Hospitals and Clinics of Minnesota
2525 Chicago Avenue South, Minneapolis, MN  55404

Assent Form for Child or Adolescent Ages 7-17 with Type II or Type III PPB

We are asking you to take part in a research study because you have pleuropulmonary blastoma (PPB). PPB is a rare type of cancer in the lung. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we want to learn more about PPB and how to treat it. We will do this by collecting records on how doctors treat children with Types II & III PPB. Based on past experiences, the Registry makes suggestions on how PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want your permission as well. Children and teens with Types II and III PPB will be treated with surgery and chemotherapy. Some may also need to receive radiation therapy. Chemotherapy is a type of strong medicine that destroys cancer cells. Radiation therapy uses strong x-rays to destroy cancer cells. Chemotherapy and radiation therapy can also cause side effects that could make you temporarily feel sicker.

As part of a Registry, information about your illness and how you respond to treatment is sent to the main PPB Study research office. Doctors from around the world want to share information about treating children and teenagers who have PPB. By sharing information, we can more quickly learn the best ways to treat cancer. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also receive a sample of the tumor that was removed from your chest so that they can learn in the future about how and perhaps why PPB cancers exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it.

Your mother or father or guardian can help you decide whether to agree to this scientific Registry. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.
Please answer the following questions by circling either YES or NO and entering your initials.

1. My tissue may be sent to the PPB Study office to be used in research about PPB.
   YES  NO  Initials _______

2. My leftover tissue may be kept by the PPB Study office for use in future research studies.
   YES  NO  Initials __________

3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.
   YES  NO  Initials _______

I agree to take part in this study.

Assent by child/adolescent Date

To the professional:
If the child does not sign the form but you believe the child has actively assented, please document on this form. State the specific behaviors (child shook head yes, child said “OK” after I described procedure, etc.).

______________________________________________________________________________

______________________________________________________________________________

______________________________________________________________________________

Physician/Researcher obtaining consent Date

IRB# 0909-082  Initial IRB Approval: 12/22/2009
Current IRB approval: 07/22/2015
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________
Please print (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________
Hospital Name: ____________________________________________________

The following information is requested:

- Hospital discharge summaries
- Pathologist’s reports on surgical specimens, bone marrow, CSF
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
- Treatment records (chemotherapy, radiation therapy, including chemo roadmaps)
- Consultations
- Pediatric Oncology CLINIC records
- Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
- Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.
Telephone: 612 813 7115
Fax: 612 813 7108
E-mail: gretchen.williams@childrensmn.org

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

____________________________________________    _____________________________
Printed Name of Parent or Guardian      Date Signed

____________________________________________    _____________________________
Signature of Parent or Guardian      Relationship to Patient

_____________________________________     _____________________________
Parent or Guardian Home Phone      Parent or Guardian Work Phone
Health Insurance Portability and Accountability Act (HIPAA)
Authorization to Use/Disclose Protected Health Information for Research

The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects you and your child’s individually identifiable health information (protected health information). The privacy law requires you or your child to sign an authorization in order for researchers to be allowed to use or disclose your/your child’s protected health information for research purposes in the study entitled International PPB Treatment Study.

What protected health information may be used or disclosed?

Your/your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, tumor measurement, x-rays and scans, and pathology results
- Results of tests to monitor for side effects including hearing tests, heart tests, lung tests, learning ability
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

What will your or your child’s protected health information be used for?

The main reason to use your or your child’s health information is to be able to conduct research into PPB treatments and into scientific, biologic research on PPB. PPB is a very rare malignant disease in the lung of young children. It occurs in three forms: Types I, II, and III PPB. Because it is so rare, consistent treatment of a large group of children has never occurred, and treatment success is therefore very difficult to judge. In addition, PPB appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment Study has three purposes:

1. For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease in the chest. This study collects information on
treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

2. For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

3. To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on PPB children and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store PPB tissue.

In addition to these PPB research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

Who may disclose your/your child’s protected health information to the researchers?

If you agree to your child’s participation in this PPB study, the study researchers and their staff may obtain your or your child’s protected individual health information from Children’s Hospitals and Clinics of Minnesota.

With whom would the protected health information be shared?

Your/your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child’s hospital who not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payee, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital

PPB HIPAA Authorization Form for Children's Hospitals & Clinics of MN Int’l PPB Treatment and Biology Registry
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What is the potential for re-disclosure of your/your child’s protected health information?

All reasonable efforts will be used to protect the confidentiality of your or your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your or your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your or your child’s confidentiality will be compromised.

What happens if I do not sign this permission form?

If you do not sign this permission form, your child will not be a part in this PPB research study for which your child is being considered.

For how long will you/your child’s protected health information be used or shared with others?

There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

What are your or your child’s rights after signing this Authorization form?

You/your child have the right to withdraw from participating in this research. You have the right to revoke in writing your permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your permission to conduct the research and related activities such as oversight. Even if you revoke your permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If you wish to withdraw your permission, contact the investigator and you will be asked to complete a written form.

You have the right to choose not to sign this form. If you decide not to sign, your child will not participate in this PPB research. Refusing to sign will not affect the current or future care you/your child receives at your treatment institution and will not cause any penalty or loss of benefits to which you are otherwise entitled.

If you/your child choose to share private health information with anyone not directly related to this research, the federal law designed to protect your privacy may no longer protect the shared information.

What are you/your child’s rights to access your/your child’s protected health information?

Subject to certain legal limitations, you have the right to access your child’s protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. You may access this information only after the study analyses are complete. To request this information, you will need to contact your child's doctor or the Institutional Review Board at Children’s Hospitals and Clinics of Minnesota. Findings from future research using material stored in the tissue bank established in this study (PPB tissue from your child will not be available to you.

PPB HIPAA Authorization Form for Children's Hospitals & Clinics of MN
Int’l PPB Treatment and Biology Registry
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By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this PPB study to use and disclose your/your child’s protected health information for the purposes described above. You also permit you/your child’s doctors and other health care providers to disclose you/your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at Children’s Hospitals and Clinics of Minnesota.

CERTIFICATIONS AND SIGNATURE SECTION

I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed.

Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject) OR Research Subject’s Authorized Representative (such as Parent or Guardian)   Date

Printed name of Research Subject’s Authorized Representative   Representative’s relationship to Research Subject (for example: “mother” or “father” or “guardian”)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):

IRB# 0909-082   Initial IRB Approval: 12/22/2009
               Current IRB approval: 07/22/2015
TAKING PART IN GENETIC RESEARCH: ISSUES TO CONSIDER

You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

Considering Possible Benefits
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

Considering Possible Risks
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child’s point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

Insurance Coverage
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

Employment or Other Qualification Decisions
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

Emotional Effects of Genetic Information
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
- what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
- if the researcher will keep other information with the sample
- if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
- What is the purpose of the study?
- What is my doctor's involvement in the study?
- Who is paying for the study?
- Will I be able to get the information from the genetic testing?
- Will anyone else get the information from the genetic testing?
- Will the information from the study help me or my child?
- Will the information from the study help other people with this disease or condition?
- How are the costs of the study being paid, and will my insurance company be billed?
- Will the information be in my or my child’s medical record?
- What will happen to the sample after the study is done, and do I have any control of that?
- Will any other information be kept with the sample?
- Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child's physician if you have questions or concerns. You may also contact Children's Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child's care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
HOW IS TISSUE USED FOR RESEARCH? WHAT YOU NEED TO KNOW

You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer’s. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your gender
Your racial or ethnic group
Your age
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
Treatment you have received
Your family history
Your medical history.

**How is my privacy protected?**
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

**What are the risks to me if I give my tissue to research?**
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

**Can I change my mind?**
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

**What if I have more questions?**
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
NOTICE OF PRIVACY PRACTICES

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry’s legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to “you” or “your” in this Notice, we refer to the patient. When we refer to types of disclosures of information to “you,” we mean disclosures to the patient, the patient’s guardian, or the person legally authorized to receive information about the patient.

YOUR PRIVACY RIGHTS

Confidential communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke your written permission (authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment and Biology Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

This Treatment and Biology Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

OTHER USES AND DISCLOSURES

Research: This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain
files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small. In some cases, where there is only a minimal risk to your privacy (for example, a research project comparing the treatment and outcome of all patients who received chemotherapy for PPB) we may disclose information about you without your written authorization. We will only disclose information about you for research without your authorization when the approval process determines that there is only a minimal risk to your privacy, and we have initiated steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your health. While this Registry may give them certain details about your child’s or your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Correspondence: If you have indicated on the consent form that yes, you will allow the PPB Treatment and Biology Registry to contact you with information about new studies or other Registry services that may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this contact could be by leaving messages on a home answering machine or voice mail, by email or by the Postal Service.

Other uses and disclosures: Disclosures of health information not covered by this Notice or the laws that apply to PPB Treatment and Biology Registry will be made only with your written permission.

FOR MORE INFORMATION
If you want more information about your privacy rights, are concerned that the PPB Treatment and Biology Registry has violated your privacy rights, or you disagree with a decision that we made about access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2525 Chicago Avenue South
Minneapolis, MN 55404
(612) 813-7115
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children’s and you will not be retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights
U.S. Department of Health and Human Services
233 North Michigan Avenue, Suite 240
Chicago, IL 60601
(312) 886-2359 or 1-800-368-1019
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes will apply to information we already have about you and information we receive about you in the future. We will provide an updated Notice to you when you request one. We will also post the most current Notice in public areas and on the PPB Treatment and Biology Registry Children’s Web site at www.ppbregistry.org

The effective date of this Notice is May 8, 2009.
APPENDIX VI: PPB-ASSOCIATED DISEASES CONSENTING DOCUMENTS FOR EITHER CHILDREN’S HOSPITALS AND CLINICS OF MINNESOTA OR OUTSIDE INSTITUTION
International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry
Types I, II and III PPB, and Associated Diseases

Appendix VI: Diseases Associated with PPB - Informed Consent
INTRODUCTION
You/your child are being asked to take part in The International Pleuropulmonary Blastoma Treatment and Biology Registry. Pleuropulmonary blastoma (PPB) is a rare childhood tumor of the chest. A Treatment and Biology Registry is a collection of clinical information and biological specimens (tumor tissue) from patients with PPB. An unusual feature of PPB is that in about 40% of cases, the PPB patient or other young family members have other tumors or malformations. For example, a non-cancerous kidney tumor called “cystic nephroma” is found in about 10% of families in which there is a child with PPB. There are many other conditions associated with PPB. Because PPB and the associated conditions found in PPB families suggest a familial tendency to formation of tumors, it is scientifically important to collect information on the associated conditions. In the opinion of experts in diagnosis of childhood tumors, your child has been diagnosed with _________________________________, one of the conditions which has been associated with PPB. Even though your child does not have PPB, the International PPB Registry can use its procedures to collect information on cases of conditions associated with PPB. To participate, your agreement is necessary, but it is your choice. Your child is being asked to participate because he/she has been diagnosed with a disease known to be associated with PPB.

- If you are a parent or legal guardian of a child who may be included in this Treatment and Biology Registry, your permission is required for your child to be included.

- If you are a patient with a disease associated with PPB and are old enough to consent without your parent’s permission (over age 17 years at most institutions), “your child” in this consent form refers to you.

- Depending on practices at your child’s hospital, if your child is old enough to understand some aspects of medical care (usually ages 7 to 17 years), your child’s “assent” (agreement) may be required, in addition to a parent’s consent.

This Treatment and Biology Registry has two parts:

Part 1: Collecting data on children with diseases associated with PPB. Children diagnosed with diseases associated with PPB will be treated according to decisions at
their own hospital. Information will be collected on the treatment given and on the course of the child thereafter.

**Part 2:** The second part of this study involves research into the biology of diseases associated with PPB and possible genetic causes. This involves collecting family medical history information and collecting specimens from surgeries for this condition for biological research.

Your child’s doctor can explain this research project to you. You may choose for your child to participate or not to participate. Your child can participate in Part 1 or Part 2 or both. Research like this includes only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends, family or other trusted advisors. You can also discuss it with your health care team. If you have any questions, you can ask your doctor or members of the Registry staff for more explanation.

You are considering whether or not to authorize your child’s hospital to send information on your child to The International PPB Registry, a central database about PPB and associated conditions (like your child's illness), their treatment, and the clinical course over time. Because the familial occurrence of PPB and associated conditions is rare, this kind of information is often not available in the medical literature.

This Treatment and Biology Registry is being conducted by a group of childhood cancer centers from many countries. The research is coordinated by The International PPB Registry based at Children's Hospital and Clinics of Minnesota, St Paul and Minneapolis, Minnesota USA; Barnes-Jewish and Children's Hospitals of Washington University, St Louis, Missouri USA; and Children’s National Medical Center, Washington, D. C., USA.

Patients covered by this Research Consent Form may be cared for at Children’s Hospitals and Clinics of Minnesota or at other institutions around the world.

- [ ] Your child is a patient at Children’s Hospitals and Clinics of Minnesota
- [ ] Your child is a patient at a hospital other than Children’s Hospitals and Clinics of Minnesota

**WHAT IS THE TREATMENT AND BIOLOGY REGISTRY ABOUT?**

You are being asked to take part in this study because your child has a disease associated with PPB.

1. This Registry will collect information about how diseases associated with PPB are diagnosed and treated. Cancer researchers study different types of cancer to learn more about what causes cancer, how to prevent it, how to stop it from spreading to other parts of the body, and how to cure it. The purpose of this Treatment and Biology Registry is to collect clinical information about (1) patients who have PPB and about their families, (2)
patients who have other rare childhood lung tumors or other diseases found to be associated with PPB. Your child fits in the second category. The Registry then analyzes this information (that is, does research). The results of this analysis are made available to doctors to help in the screening and care of patients with rare childhood lung tumors or the associated conditions and for research about the causes and treatment of rare lung tumors or the associated conditions.

2. **PPB Biology and Genetics**: In 30-40% of cases, children with PPB or their family members have other medical conditions. One of these conditions is lung cysts which may develop into serious cancers. The evolution of lung cysts into serious solid tumors and to certain illnesses is called the “biology of PPB”. This suggests that a genetic abnormality, such as an alteration in DNA (a mutation), predisposes some family members to PPB or other conditions and may be passed from generation to generation. A mutation (DNA abnormality) has been found in some families with PPB, but more research is needed to understand how many PPB and PPB-associated disease cases have this mutation and how it may cause the disease.

The illnesses associated with PPB are lung cysts, other cases of PPB, kidney cysts, some childhood cancers, some testicular and ovarian tumors, small bowel polyps, and several other very rare conditions. Research must be done to determine a complete list of conditions associated with PPB. Not all of these conditions are cancers. Most individuals in families with PPB are normal.

**WHAT DOES THE TREATMENT AND BIOLOGY REGISTRY INVOLVE?**

**Study Part 1: Collection of Data on Treatment of conditions associated with PPB:**

There are three major ways conditions associated with PPB might be treated:

- **Surgery** to remove cancerous and benign tumors
- **Chemotherapy** is the use of anti-cancer drugs to stop the growth of cancer cells, if there are any present
- **Radiation therapy** is the use of high-energy x-rays or other types of radiation to kill cancer cells, if there are any present

Surgery is often necessary for conditions associated with PPB. If you give your permission for your child’s tumor to be included in the Registry, information about your child’s diagnosis, age, date of birth, gender, x-rays and/or x-ray reports and digital images, surgical and pathology reports and findings, detailed family medical history, and treatment records are sent to the Registry at Children's Hospitals and Clinics of Minnesota in Minneapolis, Minnesota.

This research will collect information on how children with conditions associated with PPB are diagnosed and treated and what is their outcome.

**Study Part 2: Research into PPB Biology and Genetics:**

Much more needs to be learned about family medical histories, about the biology of PPB, and about genetic factors which might cause some cases of PPB and conditions associated with PPB.
This study asks for permission to collect family medical history information and to store excess portions of your child’s tumor(s) for research uses.

WHY IS THE TREATMENT AND BIOLOGY REGISTRY BEING CREATED?
Study Part 1: PPB and many of the conditions associated with it are very rare and there is not enough information to know whether screening for these conditions is beneficial. The goal of this research study is to collect information on how conditions associated with PPB are diagnosed and treated and analyze the information to see whether screening recommendations can be offered.

Study Part 2: Much must be learned about the biology and genetics of PPB and associated medical conditions. This study collects family medical history and establishes a collection of specimens from patients with conditions associated with PPB for research to try to answer some of these questions.

In summary, the goals of this Treatment and Biology Registry are
1) To collect data on diagnosis and treatment of conditions associated with PPB and to learn if screening recommendations will help diagnosis these conditions early.

2) To collect family medical histories and to collect and save surgery samples from individuals with conditions associated with PPB to learn more about the biology of PPB and genetic factors in PPB and its associated conditions.

HOW MANY PEOPLE WILL TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?
All patients diagnosed with rare childhood lung tumors or the associated conditions are eligible to be a part of this Treatment and Biology Registry. It is estimated that 20 – 30 new patients are diagnosed with rare childhood lung tumors or the associated conditions each year around the world and are eligible to be part of the Registry.

WHAT WILL HAPPEN IF MY CHILD IS A PART OF THE TREATMENT AND BIOLOGY REGISTRY?
Study Part 1: Diagnosis and treatment of conditions associated with PPB: Whether your child is a part of this research or not, your child’s physicians will use their best judgment to evaluate and treat your child: if surgery is required and what follow up is needed. This research will collect information about your child and how the condition associated with PPB is diagnosed and treated. This also involves collecting x-rays and tissue from surgery to review and confirm the condition.

Study Part 2: Biology and Genetics of conditions associated with PPB: The biology and genetic studies of this research involve the following biological samples:
• From the child with the PPB-associated condition:

After all diagnostic requirements are satisfied, saving part of any extra tumor tissue removed at surgery for research studies. In addition, family medical history information will be collected. Additional information on Part 2 of this research is found later in this Consent Form.
Part 1: Collection of Data on Treatment of conditions associated with PPB

HOW LONG WILL MY CHILD BE IN THE TREATMENT AND BIOLOGY REGISTRY?  
Your child will be followed indefinitely in order to determine the outcome of conditions associated with PPB.

Tissue from surgery will be saved indefinitely to be used for research into causes and treatment of PPB and associated conditions of PPB.

CAN MY CHILD STOP BEING IN THIS TREATMENT AND BIOLOGY REGISTRY?  
Yes. You can decide for your child to stop being a part of this Registry at any time. Inform the Treatment and Biology Registry and tell your child’s doctor that you wish to withdraw permission to participate. Contact information is given in other parts of this consent form. Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

(If your child ceases to be part of this study, it will not be possible to remove your child’s information from summaries of study data already incorporated into scientific presentations or publications. Future investigations and study summaries will not include your child.)

WHAT ARE THE RISKS TO MY CHILD OF BEING PART OF THE TREATMENT AND BIOLOGY REGISTRY?  
There are no specific medical risks to your child to be included in this Treatment and Biology Registry. Your child will receive the same medical care from the doctors and hospital regardless of whether he or she is part of this Registry. There is a slight risk that, because your child’s medical record is shared with this Registry, a loss of confidentiality may occur. Many steps are taken to keep all personal information confidential, as described below.

ARE THERE BENEFITS TO TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?  
There is no immediate or direct benefit from being included in this Treatment and Biology Registry. Indirectly, having your child's medical data in the Registry will help physicians and researchers learn more about PPB and its associated conditions. The information may be helpful in the diagnosis and treatment of PPB, and conditions associated with PPB, in the future. Also, study of biologic specimens in this Treatment and Biology Registry may improve understanding of what causes PPB and the associated medical conditions, how to detect them sooner, how to predict susceptible individuals in families, and perhaps how to treat such tumors in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THE TREATMENT AND BIOLOGY REGISTRY?  
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of patients with PPB and its associated conditions for evaluation of the results of their diagnosis and treatment and for studies of the biology and genetics of PPB. There is no other group in the world trying to do this for PPB. Not participating in this or any such research is an alternative available to you.

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If you choose not to participate, it will not have any effect on the care that your child will receive from your child’s doctor or hospital.

**HAS MY CHILD’S DOCTOR AND HOSPITAL APPROVED THE TREATMENT AND BIOLOGY REGISTRY?**

When research for a childhood condition study spells out exactly how a disease is to be treated, each participating hospital is required to review and approve the study before its patients are asked whether they will participate in the research treatment. This PPB Treatment and Biology Registry does not spell out how children with associated conditions of PPB are to be treated (your child’s doctor and his or her colleagues make those decisions), so it is not mandatory that this Registry has been reviewed and approved at your child’s hospital. Even though it may not be mandatory, some hospitals do choose to formally review a project like this.

This PPB Treatment and Biology Registry project has been approved at the children’s hospitals in Minnesota, Missouri, and Washington, D.C. who are coordinating the research.

Regardless of whether your child’s doctor and hospital have specifically approved this research project, your consent to participate is required. Many institutions encourage parents to consider participation in registries like this for rare diseases because it is the only practical way that information on a large group of children with a rare disease is collected.

**WILL MY CHILD’S MEDICAL INFORMATION BE KEPT PRIVATE?**

We will do our best to make sure that the personal information in your child’s medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in the files and the computer records with randomly-assigned Registry case numbers. If information from this Registry is published or presented at scientific meetings, your child’s name and other personal information will not be used. We cannot guarantee total privacy, but the chance that personal information will be given to someone else is very small.

The Privacy Practices of this Treatment and Biology Registry are attached to the end of this consent form.

**WHAT ARE THE COSTS OF TAKING PART IN THE TREATMENT AND BIOLOGY REGISTRY?**

There is no cost to participants in this research. You and your child will receive no payment for taking part in this Treatment and Biology Registry.

**WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?**

Taking part in this Treatment and Biology Registry is voluntary. You may choose for your child not to take part, and you may withdraw your child from the Registry at any time. The health care your child will receive at your local hospital will be the same whether or not you choose to take part in the Registry or choose to withdraw at a later time.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

1. If your child is a patient at Children’s Hospitals and Clinics of Minnesota:

You may contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz 612-813-7115 or krisann.schultz@childrensmn.org.

If you have any questions about your rights as a research participant or any complaints that you feel you cannot discuss with the investigators, you may call the Institutional Review Board Administrator at Children’s Hospitals and Clinics of Minnesota 612- 813-7646.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Family Relations Liaison at 612-813-7393.

2. If your child is NOT a patient at Children’s Hospitals and Clinics of Minnesota:

You can talk to your local doctor about any questions or concerns you have about this research. Your child’s physician may direct you to a local Research or Ethics Board administrator at your hospital who can also help you. You may also choose to discuss participation with support personnel at your child’s hospital, such as social workers or family support counselors.

You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at 612-813-7646 in Minneapolis, Minnesota USA.
CONSENT TO PARTICIPATE and SIGNATURES

You are asked to consent separately to Parts 1 and 2 of this Treatment and Biology Registry.

**Part 1: Collection of Information on condition associated with PPB**

I have been given a copy of this consent form. I have read it or it has been read to me. I understand the information and have had my questions answered.

My child has a condition associated with PPB. I agree to have my child be a part of the Treatment and Biology Registry Part 1: Collection of Information.

**PATIENT’S NAME ________________________________**

*Printed*

Parent/legal guardian ___________________________ ___________________________

*Print name*               Signature

Relationship to patient: __________________ DATE _____________________

Please also answer this question:

Researchers studying PPB and its associated conditions would like your permission to be able to contact you in the future if new PPB-related research topics are identified for which your participation would be helpful.

Do you agree to be contacted in the future about additional, special PPB-related research studies?

(You do not need to agree to this.)

_____ I agree to be contacted in the future       _____ I do not agree to be contacted in the future

**IF YOU AGREE:**

Name: ________________________________________

Address: ________________________________________

City, State, Postal/Zip Code: ___________________________

Telephone Number: _____________________________

Email address: ________________________________

**Physician/Researcher obtaining consent**       **Date**
Part 2: Collection and Storage of Biologic Specimens for Research

PPB “BIOLOGY RESEARCH”
This section of this consent form is about research studies on the biology of PPB-associated conditions and possible genetic factors which may be responsible for some cases of PPB and PPB-associated conditions. These research activities are separate from collecting data on how diseases associated with PPB are diagnosed and treated.

We ask that the patient with a PPB-associated condition and the child’s mother and father be a part of this research. You may take part in or decline to take part in these additional studies.

(Your child can be enrolled in Part 1 for the data collection of PPB-associated conditions, even if you say “no” to taking part in Part 2 for PPB Biology research. Alternatively, you and your child can participate in biology studies without taking part in Part 1 on PPB-associated conditions Diagnosis and Treatment.)

WHAT DOES THIS PPB-ASSOCIATED CONDITIONS TREATMENT AND BIOLOGY RESEARCH INVOLVE?
We are asking your permission to do the following:

9. To collect your family’s medical history – recording medical information on your children and relatives to include usually individuals in 2-4 generations of your family.

10. To save leftover tissue (if available) from your child’s surgery. This will be stored in a tissue bank, which is a laboratory where tumor and other specimens are kept for research studies.

Specimens saved in this Biology Registry will be used to learn many details about PPB-associated conditions cells as well as normal cells that might surround other cells. This involves looking at chemicals and perhaps genes (DNA) inside the tissue and trying to learn exactly how cells from the PPB-associated condition might be different from normal tissue. DNA from PPB-associated conditions tissue will be investigated to determine if any consistent changes can be found which might be part of the cause of PPB and related medical conditions. The results of this research will not be put in your child’s or your health records.

Your child’s tissue from the PPB-associated condition will be used only for research and will not be sold. The research done with these specimens may help to develop new products in the future.

Before you decide whether to be a part of this PPB Treatment and Biology Registry, here is some additional information:

WHY IS THIS RESEARCH BEING DONE?
PPB is an unusual childhood cancer because it is associated with other conditions in the patient or in family members in about 40% of cases. These findings suggest that in some PPB cases and in some families in which a child has PPB, a genetic factor predisposes family members to PPB and various PPB-related conditions. Much more needs to be learned about family medical histories and about the cause of PPB and how often a familial predisposition exists. The purpose of the biology studies is to collect family histories and to collect samples which can be used for
research into familial patterns of PPB and related diseases. Histories and samples will be stored indefinitely for research uses by investigators who have ideas approved by a research committee associated with this PPB Treatment and Biology Registry. Research will be performed in various laboratories. The results of these studies will not directly affect your child’s treatment, and therefore the results of the tests will not become part of your child’s health records. In the future, people who do research on these specimens may need to know more about your family’s health. While this Registry may give them certain details about your child’s or your family’s health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Also, it is important that you understand that because of the research nature of these tests, the results will not be available to you or to your child’s study doctors.

You may choose to be a part of this PPB Biology Research or not to be a part. Your decision will not affect your child’s health or treatment.

HOW LONG WILL SPECIMENS AND RECORDS BE SAVED FOR BIOLOGY RESEARCH?
Tissue from PPB-associated conditions and family medical histories will be saved indefinitely.

CAN MY CHILD OR I STOP BEING PART OF THIS TREATMENT AND BIOLOGY REGISTRY?
Yes. You can inform the PPB Registry and/or your child’s doctor at any time that you no longer wish to have tissue or medical histories be used in this PPB Treatment and Biology Registry. Contact information is given in other parts of this consent form. If you decide you no longer wish to participate in this research your child’s or your specimens and histories will no longer be used. If they have been used before that time and the results have been included in summaries or publications, it will not be possible to remove that data.

Your child’s physician will continue to care for your child regardless of a decision to withdraw from this Registry.

ARE THERE ANY ALTERNATIVES IF I DO NOT TAKE PART IN THIS TREATMENT AND BIOLOGY RESEARCH?
You may choose to take part in this research or not to take part. This Treatment and Biology Registry is attempting to collect a large group of research participants and there is no other group in the world trying to do this for PPB or PPB-associated conditions. It is possible that your child’s doctor or hospital is doing some biology research on tissue from PPB-associated conditions and we would encourage you to consider participating if it is available and you decide to do so. Not participating in this or any such research is an alternative available to you.

ARE THERE ANY BENEFITS?
There is no direct benefit to you or your child from participating in the PPB Treatment and Biology Research Registry. The benefits of research using these specimens include the possibility of learning more about what causes PPB and other diseases, how to prevent them, and
how to treat them. What might be learned may benefit others in the future and is not likely to be of benefit to your child.

Participants in this study will not be paid to participate, nor will they profit from any new product developed from research done on their specimens.

ARE THERE ANY RISKS?
The greatest risk to you or your child is unintended release of personal, private information from your health records. We will do our best to make sure that your personal information will be kept private. Information is kept in locked offices and on password-protected computers. The chance that personal information will be given to someone else is very small.
WHERE CAN I GET MORE INFORMATION ABOUT THIS RESEARCH ON HOW TISSUE IS USED FOR RESEARCH?
If you have any questions, please talk to your doctor or other patient support personnel at your child’s hospital.

You may also contact the Treatment and Biology Registry coordinating office at Children’s Hospitals and Clinics of Minnesota with questions: Dr. Kris Ann Schultz 612-813-7115 or krisann.schultz@childrensmn.org. You may also call the Children’s Hospitals and Clinics of Minnesota Institutional Review Board Administrator at 612-813-7646 in Minneapolis, Minnesota USA.

A document called "How is Tissue Used for Research?" is attached to this consent form.

MAKING YOUR CHOICE ABOUT PARTICIPATING IN THE PPB TREATMENT AND BIOLOGY REGISTRY
One parent can authorize participation of a child in Part 2: the PPB-associated conditions Treatment and Biology Research Registry. Please read the information below and think about your choices. No matter what you decide to do, it will not affect your child’s care.

Consent for Participation in PPB Biology Registry Research:
Family Medical History and Saving Surgical Tissue and Saliva or Blood for Research

1. Your Child’s Participation in PPB Biology Registry
   I agree to allow my child’s family medical history to be collected. I also agree to allow saliva or blood samples from my child to be collected and saved and to allow any leftover tumor tissue (if available) from my child to be saved for research studies related to conditions associated with PPB.

   Yes  No  _________________________  __________________
       Signature of parent/guardian              relationship to patient

                                    ______________________
                                    Date

2. PPB Patient’s MOTHER’S Participation in PPB Biology Registry
   I agree to allow my family medical history to be collected. I also agree to allow my saliva or blood samples to be collected and saved for research studies related to conditions associated with PPB.

   Yes  No  ____________________________    _____________________
       Signature of MOTHER          Date

3. PPB Patient’s FATHER’S Participation in PPB Biology Registry
   I agree to allow my family medical history to be collected. I also agree to allow my saliva or blood samples to be collected and saved for research studies related to conditions associated with PPB.

   Yes  No  ____________________________   _____________________
       Signature of FATHER            Date

IRB# 0909-082                       Initial IRB Approval: 12/22/2009
Assent Form for Child or Adolescent Ages 7-17 with an Associated Condition of PPB

The International Pleuropulmonary Blastoma (PPB) Registry

We are asking you to take part in a research study because you have the diagnosis of a medical condition sometimes associated with a rare childhood chest tumor called pleuropulmonary blastoma (PPB). PPB is very rare type of cancer in the lung and it is sometimes found to be associated with other medical conditions. Because of the rarity of this situation, your doctors want to share your case with other doctors who are collecting information on PPB and the associated conditions. A research study is when doctors work together to try out new ways to help people who are sick. This study wants to learn more about PPB and the conditions associated with PPB, how a diagnosis is made and how the disease is treated. We will do this by collecting records on how doctors treat children with PPB and conditions associated with PPB. Based on past experiences, the Registry makes suggestions on how these conditions associated with PPB might be treated but your doctors will decide on your specific treatment plan and will discuss it with you and your parents.

We have been talking with your parent(s) about this study. We need their permission to collect information on the treatment your doctor recommends. We want to include you as well. Children and teens with diseases associated with PPB who are part of this study may be treated with surgery. Your doctor will decide how best to diagnosis and treat your condition and will discuss it with your parents and you.

As part of a study, information about your illness and any surgery and other possible treatments is sent to the main PPB Study research office. Doctors from around the world want to share information about diagnosing and treating children and teenagers who have diseases associated with PPB. By sharing information, we can more quickly learn the best ways to diagnose and treat these conditions. We do not keep your name on any papers we collect. Instead, we use a number and your identity is safe.

With your permission, researchers will also send receive a sample of tissue that was removed so that they can learn in the future about how and perhaps why diseases associated with PPB exist. The sample will come from your surgery, so there will be no extra procedure needed to collect it.

Your mother or father or guardian can help you decide whether to agree to this scientific study. Please talk this over with them. And please ask your doctor if you have questions. You and your parents have a choice about taking part in the study. If you choose to be part of this study now but later decide you don’t want to be anymore, you can talk to your parents about withdrawing.
from this study. If you want to withdraw from this study you can do so and it won’t affect your right to get other treatments and services. No one will be mad or upset with you.

Please answer the following questions by circling either YES or NO and entering your initials.

1. My child’s tissue may be sent to the PPB Study office to be used in research about conditions associated with PPB.
   
   YES  NO  Initials ____________

2. My child’s leftover tissue may be kept by the PPB Study office for use in future research studies.
   
   YES  NO  Initials ________

3. Someone from the PPB Study office may contact me in the future to ask me to take part in more research.
   
   YES  NO  Initials ____________

I agree to take part in this study.

Assent by child/adolescent  ___________________________  Date

To the professional:
If the child does not sign the form but you believe the child has actively assented, please document on this form. State the specific behaviors (child shook head yes, child said “OK” after I described procedure, etc.).

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Physician/Researcher obtaining consent  ___________________________  Date

IRB# 0909-082  Initial IRB Approval: 12/22/2009
AUTHORIZATION FOR RELEASE OF INFORMATION

INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY

Patient Name: ______________________________________ Date of Birth: __________________

Please print (mo / day / year)

I authorize the following to release clinical and laboratory information on my child named above:

Doctor’s Name: ____________________________________________________

Hospital Name: ____________________________________________________

The following information is requested:

- Hospital discharge summaries
- Pathologist’s reports on surgical specimens, bone marrow, CSF
- Surgical/operative reports
- Radiology reports (x-ray, CT scan, MRI scan, bone scan etc) and/or copies of x-ray films, scans, electronic files
- Treatment records (chemotherapy, radiation therapy, including chemo roadmaps), and Pediatric Oncology CLINIC records, if applicable
- Consultations
- Pathology specimens for confirmation of diagnosis and enrollment in PPB Registry
- Family medical history including family medical history diagram

Please send the requested information to:

The International PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, Minnesota 55404, U. S. A.

Telephone: 612 813 7115       Fax: 612 813 7108

E-mail: gretchen.williams@childrensmn.org

I understand that the information in my (my child’s) health record may include information relating to sexually transmitted diseases, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV). It may also include information about behavioral or mental health services, child abuse and treatment for alcohol and drug abuse.

This Authorization does not have an expiration date, but I understand that I have a right to revoke this authorization at any time. I understand that if I stop this authorization, I must do so in writing to the PPB Registry. I understand that stopping this authorization will not apply to information that has already been released or disclosed.

I understand that authorizing the release of this health information is voluntary. I can refuse to sign this authorization. I understand that I may inspect or copy the information to be used or disclosed. I understand that any disclosure of information carries with it the potential for redisclosure and the information may not be protected by federal privacy rules.

____________________________________________    _____________________________
Printed Name of Parent or Guardian      Date Signed

____________________________________________    _____________________________
Signature of Parent or Guardian      Relationship to Patient

Address             City       State          Zip Code

_____________________________________     _____________________________
Parent or Guardian Home Phone      Parent or Guardian Work Phone
The United States privacy law (Health Insurance Portability and Accountability Act [HIPAA]), protects your child’s individually identifiable health information (protected health information). The privacy law requires you to sign an authorization on behalf of your child in order for researchers to be allowed to use or disclose your child’s protected health information for research purposes in the study entitled, **International PPB Treatment and Biology Study**.

**WHAT PROTECTED HEALTH INFORMATION MAY BE USED OR DISCLOSED?**

Your child’s individual health information that may be used or disclosed in the conduct of this research includes:

- Initials, date of birth, zip code, country of residence, race, ethnic background
- History and diagnosis of your disease
- Specific information about the treatment you received including previous treatment(s) you have had
- Results of physical exams, surgical procedures
- Information about other medical conditions that may affect your treatment
- Medical data, including lab test results, x-rays and scans, and pathology results
- Information on side effects you may experience and how these were treated
- Long-term information about your general health status and the status of your disease

**WHAT WILL YOUR CHILD’S PROTECTED HEALTH INFORMATION BE USED FOR?**

The main reason to use your child’s health information is to be able to conduct research into the conditions associated with PPB and into scientific, biologic research on PPB and PPB related conditions. PPB is a very rare malignant disease in the lung of young children and it appears to be associated with a number of other unusual medical conditions (such as kidney cysts) and appears to be genetically determined in some cases. Again, because PPB is so rare, the full extent of diseases associated with it is not known. The genetic cause and prevalence of a possible genetic disease is also not known. The International PPB Treatment and Biology Study has three purposes:

(7) For the earliest form of PPB, Type I PPB, there is no consensus on whether chemotherapy is useful after surgical removal of the disease in the chest. This study collects information on treatments for Type I PPB selected at the pediatric cancer institution where the PPB child is treated.

(8) For more advanced PPB, Types II and III PPB, it is necessary to use surgery and chemotherapy to attempt to cure the child. However, no consistent chemotherapy program has ever been evaluated in a large group of children. This study recommends a...
specific four-drug chemotherapy schedule for PPB treatment after surgery. (In some children, this therapy is used before surgery to shrink large tumors, and then it is continued after surgery.) Radiation therapy may be used if deemed necessary by doctors at the child’s treatment institution. Data will be collected in this study on the surgery, pathology, chemotherapy, radiation therapy if used, and outcome of the child’s PPB.

(9) To collect information on diseases associated with PPB and to evaluate possible genetic factors which might cause PPB, this study will collect family medical history information on children with diseases associated with PPB, and their families. Also, a PPB biologic specimen’s tissue bank will be established to collect and store tissue of children with PPB-related conditions.

In addition to these PPB and PPB-related research activities, protected health information is shared when necessary to ensure that this research meets legal, institutional and accreditation standards. This information may also be shared to report adverse events (complications of therapy) or situations that may help prevent placing other individuals at risk. Other reasons include treatment, payment or health care operations.

WHO MAY DISCLOSE YOUR CHILD’S PROTECTED HEALTH INFORMATION TO THE RESEARCHERS?
If you agree to your child’s participation in this study, the study researchers and their staff may obtain your child’s protected individual health information from the hospital and clinic where your child is treated.

WITH WHOM WOULD THE PROTECTED HEALTH INFORMATION BE SHARED?
Your child’s protected health information may be shared with the following:

- National Cancer Institute
- Food and Drug Administration
- Other regulatory agencies involved in keeping research safe for people
- Office of Human Research Protections
- The PPB Treatment and Biology Registry collaborators at Washington University, St. Louis, MO, and Children’s National Medical Center, Washington DC.
- Clinical staff at your child’s hospital who are not involved in the study but who may become involved in your or your child’s care, if it is potentially relevant to treatment
- To your health insurer or payer, if necessary, in order to secure their payment for any covered treatment not paid for through the research
- The Institutional Review Board (Human Subject’s Committee; Helsinki Committee; Ethics Review Board) at your child’s hospital

WHAT IS THE POTENTIAL FOR RE-DISCLOSURE OF YOUR CHILD’S PROTECTED HEALTH INFORMATION?
All reasonable efforts will be used to protect the confidentiality of your child’s protected health information. This information may be shared with others to support this research, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the protected health information may share it with others if the
law requires them to, and they may share it with others who may or may not be required to follow the federal privacy rule. Although there are individuals with whom your child’s protected health information must be shared as noted in this paragraph and in the previous section of this form, it is not likely that your child’s confidentiality will be compromised.

WHAT HAPPENS IF I DO NOT SIGN THIS PERMISSION FORM?
If you do not sign this permission form, your child will not be a part in this research study for which your child is being considered.

FOR HOW LONG WILL YOUR CHILD’S PROTECTED HEALTH INFORMATION BE USED OR SHARED WITH OTHERS?
There is no scheduled date at which this information will be destroyed or no longer used. This is because information that is collected for research purposes continues to be analyzed for many more years. It is not possible to determine when this will be complete. Because of this, this authorization does not have an expiration date.

WHAT ARE MY CHILD’S RIGHTS AFTER SIGNING THIS AUTHORIZATION FORM?
Your child has the right to withdraw from participating in this research. Your child has the right to revoke in writing his or her permission for use or sharing the protected health information acquired during this research, except to the extent that the investigators have already relied on your child’s permission to conduct the research and related activities such as oversight. Even if your child revokes permission, institutions involved in this research’s may preserve and use or disclose information needed for the integrity of the study. Once permission is withdrawn and your child is no longer participating in the study, no further private health information on your child will be acquired. If your child wishes to withdraw permission, he or she should contact the investigator and your child will be asked to complete a written form.

Your child has the right to choose not to sign this form. If your child decides not to sign, your child will not participate in this research. Refusing to sign will not affect the current or future care your child receives at his or her treatment institution and will not cause any penalty or loss of benefits to which your child is otherwise entitled.

If your child chooses to share private health information with anyone not directly related to this research, the federal law designed to protect your child’s privacy may no longer protect the shared information.

WHAT ARE MY RIGHTS TO ACCESS MY CHILD’S PROTECTED HEALTH INFORMATION?
Subject to certain legal limitations, your child has the right to access his or her protected health information that (1) is created during this research that relates to treatment or payment provided and (2) is not exempted under certain laws and regulations. Your child may access this information only after the study analyses are complete. To request this information, your child will need to contact his or her doctor or the Institutional Review Board at their hospital. Findings from future research using material stored in the tissue bank established in this study (tissue from your child) will not be available to you.
By signing this form, you authorize your child’s doctor and his/her assistants and the research team managing this study to use and disclose your child’s protected health information for the purposes described above. You also permit your child’s doctors and other health care providers to disclose your child’s health information for the purposes described above.

If you have not already received a copy of your hospital’s “Privacy Notice”, you may request one. If you have any questions or concerns about your child’s privacy rights, you should contact your child’s doctor or the Institutional Review Board or Patient Privacy Office at your child’s hospital.

**CERTIFICATIONS AND SIGNATURE SECTION**

I am the research subject (patient) or am authorized to act on behalf of the subject. I have read this information, and I will receive a copy of this authorization form after it is signed.

--------------------------------------
Printed Name of Patient (Research Subject)

Signature of Patient (Research Subject) OR Research Subject’s Authorized Representative (such as Parent or Guardian)  Date

--------------------------------------
Printed name of Research Authorized Representative  Subject’s Representative’s relationship to Research Subject (*for example: “mother” or “father” or “guardian”*)

Please explain Authorized Representative’s relationship to the Patient (Research Subject) and include a description of the Representative’s authority to act on behalf of the subject (*for example: “patient’s parent; patient too young to sign for self” or “patient’s legal guardian; patient too young to sign for self”):

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IRB# 0909-082  Initial IRB Approval: 12/22/2009
You have been asked if you and/or your child would like to take part in a genetic research study. As in all research studies, you should think carefully about the risks and benefits to your child and yourself. Because genetic information is fairly new and may be used in ways we do not yet know of, there are some special issues to think about.

**Considering Possible Benefits**
You should be sure to understand what benefits the knowledge obtained in this study might have for you or your child. Those might include better understanding the causes of disease or of how the disease relates to treatment options. You may also obtain information about whether other children or family members may be affected.

You might also wish to consider possible benefits of the research to others in the future. The practice of medicine moves forward through research.

Be sure to consider that any benefits that may exist are uncertain. If the outcome of the study were already known it would not be considered a research study.

**Considering Possible Risks**
You should also be sure to understand what harmful things might happen for you or your child. The risks like the discomfort of having a blood test are easy to understand. These are important to think of from your child's point of view.

There are also risks the information might be found out or become available to some other group or person, such as your insurance company, a future employer, or a government agency. Researchers are required to have rules about keeping the information they get private, but you need to decide if the risk of their not following those rules or of the information being accidentally released is a major concern to you.

**Insurance Coverage**
One risk if information is disclosed is on insurance coverage now or in the future. Insurers often ask about genetic diseases and might claim a genetic disease is a "pre-existing condition" which they do not need to cover. They may ask if you have had a genetic test and require you to give them that information before providing insurance. This might be true for you or your child. If this is a condition which might affect extended family members and you have shared the information with them, they might be affected.

Be sure to know if the information will be in your medical record, and therefore available to an insurance company, or if there will be a bill to your insurer for anything involved in the genetic research. You can ask that information not be in your medical record, but often Informed Consent Forms are placed in the medical record or notations about research or tests are included.

**Employment or Other Qualification Decisions**
It is possible that genetic information would be used in employment decisions in the future. Employers might consider this is making decisions about hiring, job placement or offering insurance coverage. Again, this might not happen, but is a risk. You should feel comfortable there is enough protection of your privacy in the research methods.

**Emotional Effects of Genetic Information**
You should also consider the emotional effect this information might have on you, your child, or your extended family if you get or share the information. This information might help you be more realistic. However learning of a genetic condition might cause people to change the way they think about themselves, feel less secure about themselves, or to see their children differently. It might change the way your spouse or extended family think about you. These changes might not occur, and can be dealt with in counseling, but you should think in advance about whether these are concerns for you.
Control Over Samples
Some research studies say they will destroy the sample after the research, but others intend to keep the sample in case they have future uses that they do not know of at this time. Generally, when you agree to give a genetic sample, you are losing all control of it, and you may not know how it will be used in the future. Some people are concerned about any use of their DNA, some people are comfortable with some uses like developing new medical treatments but not other uses, and some people have no concerns about how the sample may be used. It could be used by a university, company or government health agency to make money as well as to develop treatments.

You should find out
• what will happen to the sample after the specific research study is finished – will it be kept or destroyed?
• if the researcher will keep other information with the sample
• if you have any control of the sample after you initially give it (usually you do not)

These things might not happen, but there is some risk they could. This should affect both thinking about whether to take part in the research and thinking about whether the information about you gained in the research is given to you.

Some Questions You May Want to Ask
• What is the purpose of the study?
• What is my child’s doctor’s involvement in the study?
• Who is paying for the study?
• Will my child be able to get the information from the genetic testing?
• Will anyone else get the information from the genetic testing?
• Will the information from the study help me or my child?
• Will the information from the study help other people with this disease or condition?
• How are the costs of the study being paid, and will my child’s insurance company be billed?
• Will the information be in my child’s medical record?
• What will happen to the sample after the study is done, and do I have any control of that?
• Will any other information be kept with the sample?
• Do I feel comfortable the researcher and organization doing the research will comply with the privacy rules they have told me about?

Considering Possible Risks and Possible Benefits
We are not trying to encourage or discourage you from taking part in this research. These are some issues you should think about as you consider the possible benefits and harms of taking part. You should discuss these with the researcher and your child’s physician if you have questions or concerns. You may also contact Children’s Hospitals and Clinics Institutional Review Board (612-813-7646) or Office of Ethics (612-813-6159) if you wish to speak about this with someone not involved in the research project or your child’s care.

Consider as well that you are making a decision for both yourself and for your child. Sometimes people feel comfortable in making choices for themselves but are hesitant to make a choice that will have risks for their child unless they need to make that choice.

Be sure you have all the information you think you need before making the decision, think it over carefully and discuss it with people you trust. Think both about participating in the research and about having the information about you given to you. Only then can you make an informed decision about participating in the research.
HOW IS TISSUE USED FOR RESEARCH? WHAT YOU NEED TO KNOW

You have been asked to provide some of your tissue for medical research. Tissue helps researchers find new and better treatments for people. Before you make a decision to let researchers use your tissue, it is helpful to learn more.

What is tissue?
Tissue can include materials from your body such as skin, hair, nails, blood, and urine.

Why do people do research with tissue?
Research with tissue can help us prevent and treat diseases such as cancer, diabetes, and Alzheimer's. By giving your tissue, you could help researchers gain knowledge that may possibly save lives.

Your tissue may be used in all types of research, such as finding the causes of disease, developing new tests or new drugs. Your tissue may also be used for genetic research, or research looking at diseases that are passed on in families. This research will help scientists better understand how genes affect health and illness.

You do not get to decide what kind of research your tissue is used in, just as you do not get to decide who gets your blood when you donate at a blood drive. You will not profit from any of the products developed from the research. Products are not often developed from just one person's tissue. However, you will have the reward of knowing you helped researchers find new ways to prevent and treat diseases.

How do you collect the tissue that I give to research?
The tissue that you give to research is leftover tissue from a medical test, for example a blood test. Even though your doctor only takes the amount of tissue he or she needs for the medical test, there may still be some leftover tissue. Doctors usually destroy this unneeded tissue, but you may choose to allow this leftover tissue to be stored and used for future research. Regardless of your decision, it will not affect your care. Remember, your tissue cannot be used for research without your written consent.

What happens to my tissue after it is collected?
After your doctor completes all your medical tests, he or she will send the leftover tissue to a tissue bank along with some information about your general health. (A tissue bank is a place where the tissue is protected and stored.)

Will I find out the results of the research using my tissue?
You will receive the results of your medical test (e.g., biopsy, blood test), but you will not get the results of the research performed with your leftover tissue. Tissue research takes a long time and requires tissue samples from many people before results are known; results may not be ready for many years. These results do not affect your care when you donate the tissue.

Why do you need information from my health records?
In order to do research with your tissue, researchers may need to have some information about you. This information helps them learn more about specific diseases. Information that researchers ask you for may include:
Your age and gender
Your racial or ethnic group
Whether you smoke.
Researchers may also need information about:
The date of your diagnosis
Treatment you have received
How is my privacy protected?
To protect your privacy, your tissue will be coded with a random number instead of your name. Your name, address, phone number, Social Security number, date of birth, and anything else that could identify you will be removed before the records are sent to the researcher. The researcher will not be able to identify you.

The tissue bank is in charge of keeping your information private. They will take careful steps to prevent the misuse of records. People will not have access to your personal information. Tissue banks are not allowed to release your personal information without your consent.

What are the risks to me if I give my tissue to research?
There are few risks to you. The greatest risk is the release of information from your health records, but the tissue bank will protect your records so that your name, address, and phone number will be kept private. The chance of these personal facts being given to someone else is very small.

In some cases, health records can be used against patients and their families. For example, insurance companies may deny a patient insurance, or employers may not hire someone with a certain illness. However, since personal information is removed from research samples, the risk of your privacy being violated is very small.

Can I change my mind?
Yes. You can change your mind about letting researchers use your tissue at any time. Contact your doctor if you do not want your tissue to be used in any future research. The doctor will contact the tissue bank and ask them to destroy or return the rest of your tissue. However, tissue already used for research cannot be returned, and the data resulting from a study of this tissue may be used in published research. The tissue bank will return or destroy all the rest of your tissue.

What if I have more questions?
If you have any questions, talk to your doctor or nurse. Or call the research review board listed on the informed consent form.
International Pleuropulmonary Blastoma Treatment and Biology Registry

NOTICE OF PRIVACY PRACTICES

This notice of privacy practices describes how medical information about you may be used and disclosed and how you can get access to this information. Please review it carefully.

During your participation in the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry, doctors, researchers, and others will review information about your medical history and health. This information is called Protected Health Information or PHI. This Treatment and Biology Registry is required by law to:

- maintain the privacy of your protected information.
- provide you with a copy of this Notice of Privacy Practices.
- abide by the terms of our current Notice.

This Notice describes the Registry's legal duties and privacy practices as well as your rights related to your protected health information.

Most of the patients in this Treatment and Biology Registry are children. When we refer to "you" or "your" in this Notice, we refer to the patient. When we refer to types of disclosures of information to "you," we mean disclosures to the patient, the patient's guardian, or the person legally authorized to receive information about the patient.

YOUR PRIVACY RIGHTS

Confidential communication: You may request that this Treatment and Biology Registry provide you with your medical information in a confidential manner. For example, you can request that we not leave a message on an answering machine or that we send mailings to a special address. You must make this request in writing and specify a means of communication. This Treatment and Biology Registry must agree to any reasonable request that you make.

Revoke your written permission (authorization): If you have given authorization for use or sharing of your health information, you may take back that authorization, in writing, at any time. If you take back your authorization, the Treatment Registry will no longer use or share your health information for the reasons listed on your written authorization. Of course, we cannot take back any information we have already shared with your permission.

Copy of the Notice: If you ask, you may obtain a paper copy of this Notice, even if you have agreed to receive the Notice electronically.

USE AND DISCLOSURE OF YOUR MEDICAL INFORMATION

This Treatment Registry will primarily use your medical information to learn about your treatment. We may also use biology samples to learn more about PPB.

OTHER USES AND DISCLOSURES

Research: This study collects family medical history and establishes a collection of specimens from PPB patients for research to try to answer some of these questions.

We will do our best to make sure that the personal information in your child's medical record will be kept private. The Treatment and Biology Registry Offices (Minnesota, Missouri, and Washington, DC) maintain files and data in locked offices and on password-protected computers. Patient names will be replaced in
the files and the computer records with randomly-assigned Registry case numbers. If information from
this Registry is published or presented at scientific meetings, your child’s name and other personal
information will not be used. We cannot guarantee total privacy, but the chance that personal information
will be given to someone else is very small. In some cases, where there is only a minimal risk to your
privacy (for example, a research project comparing the treatment and outcome of all patients who
received chemotherapy for PPB) we may disclose information about you without your written
authorization. We will only disclose information about you for research without your authorization when
the approval process determines that there is only a minimal risk to your privacy, and we have initiated
steps to protect your privacy to the greatest extent possible.

Research will be performed in various laboratories. The results of these studies will not directly affect your
child’s PPB treatment, and therefore the results of the tests will not become part of your child’s health
records. In the future, people who do research on these specimens may need to know more about your
health. While this Registry may give them certain details about your child’s or your health, it will not give
them your name, address, phone number, or any other information that will let the researchers know who
you are.

Correspondence: If you have indicated on the consent form that yes, you will allow the PPB Treatment
and Biology Registry to contact you with information about new studies or other Registry services that
may be of interest to you, we may contact you in the future. Unless you have otherwise indicated, this
contact could be by leaving messages on a home answering machine or voice mail, by email or by the
Postal Service.

Other uses and disclosures: Disclosures of health information not covered by this Notice or the laws
that apply to PPB Treatment and Biology Registry will be made only with your written permission.

FOR MORE INFORMATION
If you want more information about your privacy rights, are concerned that the PPB Treatment and
Biology Registry has violated your privacy rights, or you disagree with a decision that we made about
access to or disclosure of medical information, you may contact the PPB Treatment and Biology Registry:

The PPB Treatment and Biology Registry
Children’s Hospitals and Clinics of Minnesota
2525 Chicago Avenue South
Minneapolis, MN 55404
(612) 813-7115
E-mail: info@ppbregistry.org

Filing a complaint will not affect the quality of the services you receive from Children’s and you will not be
retaliated against for filing a complaint. You may also file a complaint with the:

Office for Civil Rights
U.S. Department of Health and Human Services
233 North Michigan Avenue, Suite 240
Chicago, IL 60601
(312) 886-2359 or 1-800-368-1019
E-mail: OCRComplaint@hhs.gov

The PPB Treatment and Biology Registry reserves the right to make changes to this Notice. The changes
will apply to information we already have about you and information we receive about you in the future.
We will provide an updated Notice to you when you request one. We will also post the most current
Notice in public areas and on the PPB Treatment and Biology Registry Children’s Web site at
www.ppbregistry.org

The effective date of this Notice is May 8, 2009.
APPENDIX VII: TYPES I, II, & III PPB TREATMENT
REGISTRY ENROLLMENT FORM
Patient Information

Gender (1= Male; 2= Female): [ ]

Date of Birth: [____] / [____] / [____]____

Initial Diagnosis Date: [____] / [____] / [____]____

Height: [____]____ cm Weight: [____]____ . [____] kg BSA: [____] . [____] m²

Ethnicity: [ ]
1 = White
2 = Black, or African American
3 = Hispanic or Latino, incl. Mexican, Puerto Rican, Cuban, Cen. or S. American
4 = Native American, incl. Aleutian, Eskimo
5 = Asian
6 = Indian Subcontinent
7 = Arab
8 = Other, Specify: __________________________

Country where the subject resided at the time of initial diagnosis: ______________________________

Symptoms and Diagnostics at Presentation

- Patient had a pneumothorax (PTX) at the time of PPB diagnosis (1= Yes; 2= No): [ ]
- Patient had pneumonia at the time of PPB diagnosis (1= Yes; 2= No): [ ]
- Patient had a pleural effusion at the time of PPB diagnosis (1= Yes; 2= No): [ ]
  If cytology was sampled on the pleural effusion: Were the results: [ ]
  1= Negative
  2= Positive
  3= Unspecified
- Spinal fluid sampled at Diagnosis (1= Yes; 2= No): [ ]
  If yes, results =: [ ]
  1= Negative
  2= Positive
  3= Unspecified
- Bone marrow sampled at Diagnosis (1= Yes; 2= No): [ ]
  If yes, sample was [ ]
  1 = Aspirate
  2 = Trephine/Biopsy
  3 = Aspirate = Trephine/Biopsy
  Results = [ ]
  1 = Negative
  2= Positive

Were there any Unusual Metabolic Findings? (1= Yes; 2= No): [ ]

If yes, please provide specific details:
________________________________________________________________________________________________
________________________________________________________________________________________________
Symptoms and Diagnostic at Presentation (cont.)

Location of lung cyst(s). Check all that apply:

- □ Upper
- □ Mid
- □ Lower
- □ Pleura
- □ Diaphragm
- □ Unspecified

- □ Right
- □ Left

Primary Tumor Measurements: |__|__| . |__| cm  x  |__|__| . |__| cm

Method of Measurement: [|___|  1 = MRI  2 = CT Scan  3 = X-ray  4 = Other (specify: ________________________)  
                      5 = Radionuclide Scan  6 = Physical Exam  9 = Other (specify: ________________________)

Pathological tumor measurements, if available: |__|__| . |__| cm  x  |__|__| . |__| cm

Clinical or imaging evidence of regional lymph node involvement: (1= Yes; 2= No):   |__|    
If no, were nodes accessible to examination?    (1= Yes; 2= No):    |__|    

Is metastasis present? (1= Yes; 2= No):   |__|    

Clinical and Imaging Defined Metastases (1= Yes; 2= No; 9= Unknown):

Please fill in all blanks

- □ Regional lymph nodes
- □ Liver
- □ Bone
- □ Other Site (specify): _______________________________________________________

|__| Distant Nodes
□ Distant Nodes
□ Liver
□ CNS
□ Bone
□ Bone Marrow

Surgically Defined Metastases (1= Yes; 2= No; 9= Unknown):

Please fill in all blanks.

- □ Regional lymph nodes
- □ Liver
- □ Bone
- □ Other Site (specify): _______________________________________________________

□ Distant Nodes
□ Distant Nodes
□ Liver
□ CNS
□ Bone
□ Bone Marrow

Form completed by:

Name: ____________________________  : ______________________________ |__|__| / |__|__| / |__|__|__|__|
(Please print)              (Signature)      month         day           year

IPPBTBR-1      Page 2 of 2  Sept 2009
APPENDIX VIII: TYPE I PPB HYDRATION AND TREATMENT GUIDELINES, AND ROADMAPS

Type I PPB Hydration Guidelines

Pre-hydration, all courses:

D5½NS IV at 200 mL/m²/hour, until patient is adequately hydrated (urine output exceeds 2 cc/kg/hr).

Post-hydration, all courses:

Suggested hydration after Cyclophosphamide dose is D5½NS IV at 3L/ m²/hour over 24 hours.
## Dosages for patients > 3 yrs:

<table>
<thead>
<tr>
<th>Vincristine (VCR)</th>
<th>Actinomycin D (DACT)</th>
<th>Cyclophosphamide (CPM)</th>
<th>*Mesna</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>1.5 mg/m² IV push Day 0 of weeks 0 - 9 (Max. dose 2 mg).</td>
<td>0.045 mg/kg Day 0 of weeks 0, 3, 6, 9 (Max dose 2.5 mg).</td>
<td>1.2 gm/m²/dose IV as 1 hr infusion with IV fulids and MESNA, day 0 of weeks 0, 3, 6, 9.</td>
<td>Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution</td>
</tr>
</tbody>
</table>

## Dose modifications for children > 12 months but < 3 yrs of age:

| VCR: use 0.05 mg/kg | DACT: use 0.045 mg/kg | CPM: use 40 mg/kg |

## Dose modifications for children < 12 months of age:

| VCR: use 0.025 mg/kg | DACT: use 0.025 mg/kg | CPM: use 40 mg/kg |
## International Pleuropulmonary Blastoma
### Treatment and Biology Registry
#### Type I PPB Treatment Roadmap
##### Course 2 of 4

<table>
<thead>
<tr>
<th>Date Due</th>
<th>Date Given</th>
<th>Week</th>
<th>VCR</th>
<th>DACT*</th>
<th>CPM</th>
<th>*MESNA</th>
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<tr>
<td>________</td>
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<td>12</td>
<td>VCR</td>
<td>DACT*</td>
<td>CPM</td>
<td>*MESNA</td>
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<td>VCR</td>
<td>DACT*</td>
<td>CPM</td>
<td>*MESNA</td>
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<td>16</td>
<td>VCR</td>
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<td>________</td>
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<td>17</td>
<td>VCR</td>
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<td>________</td>
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<td>18</td>
<td>VCR</td>
<td>DACT*</td>
<td>CPM</td>
<td>*MESNA</td>
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<td>VCR</td>
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<td>20</td>
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<td>DACT*</td>
<td>CPM</td>
<td>*MESNA</td>
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</tbody>
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### Dosing rules:
- Use current age and size at start of each course
- **Age** mos  **Ht.** cm  **Wt.** kg  **BSA**

### Dosages for patients > 3 yrs:
- **Vincristine (VCR)** IV 1.5 mg/m² IV push Day 0 of weeks 12-21 (Max. dose 2 mg).
- **Actinomycin D (DACT)** IV 0.045mg/kg Day 0 of weeks 12, 15, 18, 21 (Max dose 2.5 mg).
- **Cyclophosphamide (CPM)** IV 1.2 gm/m²/dose IV as 1 hr infusion with IV fulids and MESNA, day 0 of weeks 12, 15, 18, 21.
- **Mesna** IV Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution

### Dose modifications for children
- **Dose modifications for children > 12 months but < 3 yrs of age:**
  - VCR: use 0.05 mg/kg
  - DACT: use 0.045 mg/kg
  - CPM: use 40 mg/kg
- **Dose modifications for children < 12 months of age:**
  - VCR: use 0.025 mg/kg
  - DACT: use 0.025 mg/kg
  - CPM: use 40 mg/kg
## International Pleuropulmonary Blastoma
### Treatment and Biology Registry
#### Type I PPB Treatment Roadmap
##### Course 3 of 4

<table>
<thead>
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<th>Date Due</th>
<th>Date Given</th>
<th>VCR mg</th>
<th>DACT mg</th>
<th>CPM mg</th>
<th>*MESNA mg</th>
<th>Comments</th>
</tr>
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</tbody>
</table>

**Dosing rules:** use current age and size at start of each course

- **Age** mos
- **Ht.** cm
- **Wt.** kg
- **BSA**

**Dosages for patients > 3 yrs:**

- **Vincristine (VCR)** IV 1.5 mg/m² IV push Day 0 of weeks 24 - 33 (Max. dose 2 mg).
- **Actinomycin D (DACT)** IV 0.045 mg/kg Day 0 of weeks 24, 27, 30, 33 (Max dose 2.5 mg).
- **Cyclophosphamide (CPM)** IV 1.2 g/m² dose IV as 1 hr infusion with IV fluids and MESNA, day 0 of weeks 24, 27, 30, 33.

*Mesna* IV Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution

**Dose modifications for children**

- **≥ 12 months but < 3 yrs of age:**
  - **VCR:** use 0.05 mg/kg
  - **DACT:** use 0.045 mg/kg
  - **CPM:** use 40 mg/kg

- **< 12 months of age:**
  - **VCR:** use 0.025 mg/kg
  - **DACT:** use 0.025 mg/kg
  - **CPM:** use 40 mg/kg
## International Pleuropulmonary Blastoma

### Treatment and Biology Registry

#### Type I PPB Treatment Roadmap

**Course 4 of 4**

<table>
<thead>
<tr>
<th>Date Due</th>
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<th>Week</th>
<th>VCR</th>
<th>DACT</th>
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<td>DACT</td>
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<td>End of Therapy</td>
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</table>

**Dosages for patients > 3 yrs:**

- **Vincristine (VCR):** IV 1.5 mg/m² IV push Day 0 of weeks 36 - 39 (Max. dose 2 mg).
- **Actinomycin D (DACT):** IV 0.045 mg/kg Day 0 of weeks 36 and 39 (Max dose 2.5 mg).
- **Cyclophosphamide (CPM):** IV 1.2 gm/m²/dose IV as 1 hr infusion with IV fluids and MESNA, day 0 of weeks 36 and 39.
- ***Mesna:** IV Use of Mesna with this dose of cyclophosphamide is the decision of the treating physician and institution.

### Dose modifications for children

- **> 12 months but < 3 yrs of age:**
  - **VCR:** use 0.05 mg/kg
  - **DACT:** use 0.025 mg/kg
  - **CPM:** use 40 mg/kg

- **< 12 months of age:**
  - **VCR:** use 0.025 mg/kg
  - **DACT:** use 0.025 mg/kg
  - **CPM:** use 40 mg/kg

**Dosing rules:** use current age and size at start of each course.

Age _____ mos   Ht. _____ cm   Wt. _____ kg   BSA ___________

**Comments**

(Entries must be dated)
APPENDIX IX: TYPE II AND IIII PPB HYDRATION, TREATMENT GUIDELINES, AND ROADMAPS

Pre-hydration for IVADo courses:

D5½NS IV at 200 mL/m2/hour, until patient is adequately hydrated (urine output exceeds 2 cc/kg/hr).
Chemotherapy:
- Vincristine IV push day 1, then weekly until (including) week 7 then every 3 weeks.
- Actinomycin IV push day 1.
- Ifosfamide (I) IV over 3 hours, days 1, 2.
- MESNA with Ifosfamide and then 3, 6, and 9 hours after the start of the Ifosfamide dose.
- Doxorubicin IV over 30 min, days 1, 2.

Pre-hydration for IVA courses:

D5½NS IV at 200 mL/m2/hour, until patient is adequately hydrated (urine output exceeds 2 cc/kg/hr).
Chemotherapy:
- Vincristine IV push day 1.
- Actinomycin IV push day 1.
- Ifosfamide (I) IV over 3 hours, day 1.
- MESNA with Ifosfamide and then 3, 6, and 9 hours after the start of the Ifosfamide dose.

Post-hydration, all courses:

D5½NS + 10 mEq KCl/L IV at 125 mL/m2/hour beginning immediately after Ifosfamide and continuing until next Ifosfamide dose or until 24 hours after last dose.
### Dosing Table

**Due** | **Given** | **Day** | **Week** | **VCR** | *IFOS* | DACT | DOXO | Mesna | **Comments**
---|---|---|---|---|---|---|---|---|---

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**Vincristine (VCR)**: IV Dose per Table, IV push Days as above.

*Ifosfamide (IFOS)*: IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**: IV Dose per Table, IV push Days as above.

**Doxorubicin (DOXO)**: IV Dose per Table, 30 minute continuous infusion, Days as above (Max. cumulative dose 375 mg/m² if no mediastinal radiation; max dose 300 mg/m² if mediastinal radiation used).

**Mesna (M)**: IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

**Dose Table**

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<td>VCR:</td>
<td>0.75 mg/m²</td>
<td>1 mg/m²</td>
<td>1.5 mg/m² (max 2mg)</td>
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<td><em>IFOS</em>:</td>
<td>1.5 gm/m²</td>
<td>2 gm/m²</td>
<td>3 gm/m²</td>
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<tr>
<td>DACT:</td>
<td>0.75 mg/m²</td>
<td>1 mg/m²</td>
<td>1.5 mg/m² (max 2mg)</td>
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<td>DOXO:</td>
<td>15 mg/m²</td>
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<td>Mesna:</td>
<td>300 mg/m²</td>
<td>400 mg/m²</td>
<td>600 mg/m²</td>
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*Substitute CPM for IFOS for all subsequent cycles if **significant** Fanconi syndrome occurs. See Protocol § A-XI: 1.2 for CPM, and Mesna with CPM, doses.*
### International Prospective Pleuropulmonary Blastoma Treatment Study

#### Preliminary Types II & III Treatment Roadmap

**Therapy: i²VADo²**

**Courses 3 & 4**

Dosing rules: use current age and size at start of each course

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**Comments**

(Entries must be dated)

**Vincristine (VCR)**

IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**

IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**

IV Dose per Table, IV push Days as above

**Doxorubicin (DOXO)**

IV Dose per Table, 30 minute continuous infusion, Days as above (Max. cumulative dose 375 mg/m² if no mediastinal radiation; max dose 300 mg/m² if mediastinal radiation used).

**Mesna (M)**

IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

**Dose Table**

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<tr>
<td>VCR: 0.75 mg/m²</td>
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<td>1.5 mg/m² (max 2mg)</td>
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<td>*IFOS: 1.5 gm/m²</td>
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<tr>
<td>DACT: 0.75 mg/m²</td>
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<td>DOXO: 15 mg/m²</td>
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<td>Mesna: 300 mg/m²</td>
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<td>600 mg/m²</td>
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**Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs.**

See Protocol § A-XI: 1.2 for CPM, and Mesna with CPM, doses.
**International Prospective Pleuropulmonary Blastoma Treatment Study**

**Preliminary Types II & III Treatment Roadmap**

**Therapy: IVA**

**Courses 5 & 6**

Dosing rules: use current age and size at start of each course

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**Vincristine (VCR)**

IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**

IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**

IV Dose per Table, IV push Days as above

**Mesna (M)**

IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

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<td>*IFOS:</td>
<td>1.5 gm/m²</td>
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<td>DACT:</td>
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<td>M:</td>
<td>300 mg/m²</td>
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*Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. See Protocol § A-XI: 1.2 for CPM, and Mesna with CPM, doses.

**Begin each course when Plt. Ct. > 100k and ANC > 1,000.**
### International Prospective Pleuropulmonary Blastoma Treatment Study

**Preliminary Types II & III Treatment Roadmap**

**Therapy: IVA**

**Courses 7 & 8**

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**Vincristine (VCR)**
- IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**
- IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**
- IV Dose per Table, IV push Days as above

**Mesna (M)**
- IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

**Dose Table**

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*Substitute CPM for IFOS for all subsequent cycles if **significant** Fanconi syndrome occurs. See Protocol § A-XI: 1.2 for CPM, and Mesna with CPM, doses.

**Begin each course when Plt. Ct. > 100k and ANC > 1,000.**
**International Prospective Pleuropulmonary Blastoma Treatment Study**

**Preliminary Types II & III Treatment Roadmap**

**Therapy: IVA**

**Courses 9 & 10**

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**Vincristine (VCR)**

IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**

IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**

IV Dose per Table, IV push Days as above

**Mesna (M)**

IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

**Dosing rules:** Use current age and size at start of each course.

**Comments**

(Entries must be dated)

**International Prospective Pleuropulmonary Blastoma Treatment Study**

**PPB Reg. ID: __________**

**Institution: __________**

**Vincristine (VCR)**

IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**

IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**

IV Dose per Table, IV push Days as above

**Mesna (M)**

IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

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**Comments**

(Entries must be dated)

**International Prospective Pleuropulmonary Blastoma Treatment Study**

**PPB Reg. ID: __________**

**Institution: __________**

**Vincristine (VCR)**

IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**

IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**

IV Dose per Table, IV push Days as above

**Mesna (M)**

IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

**Dosing rules:** Use current age and size at start of each course.

**Comments**

(Entries must be dated)

**International Prospective Pleuropulmonary Blastoma Treatment Study**

**PPB Reg. ID: __________**

**Institution: __________**

**Vincristine (VCR)**

IV Dose per Table, IV push Days as above

**Ifosfamide (IFOS)**

IV Dose per Table, IV over 3 hours, Days as above. Give with Mesna and hydration.

**Actinomycin D (DACT)**

IV Dose per Table, IV push Days as above

**Mesna (M)**

IV Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.

**Dosing rules:** Use current age and size at start of each course.

**Comments**

(Entries must be dated)
### International Prospective Pleuropulmonary Blastoma Treatment Study

**Preliminary Types II & III Treatment Roadmap**

**Therapy: IVA**

**Courses 11 & 12**

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**Comments**
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<td>Mesna (M)</td>
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<td>Dose per Table, with Ifos over 1 hour; doses 2 and 3 IV push over 3-5 min. at hours 3 and 7.</td>
</tr>
</tbody>
</table>

**Dose Table**

<table>
<thead>
<tr>
<th>Dose Table</th>
<th>&lt; 6 months</th>
<th>6 months -12 months</th>
<th>&gt; 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR:</td>
<td>0.75 mg/m²</td>
<td>1 mg/m²</td>
<td>1.5 mg/m² (max 2mg)</td>
</tr>
<tr>
<td>*IFOS:</td>
<td>1.5 gm/m²</td>
<td>2 gm/m²</td>
<td>3 gm/m²</td>
</tr>
<tr>
<td>DACT:</td>
<td>0.75 mg/m²</td>
<td>1 mg/m²</td>
<td>1.5 mg/m² (max 2mg)</td>
</tr>
<tr>
<td>M:</td>
<td>300 mg/m²</td>
<td>400 mg/m²</td>
<td>600 mg/m²</td>
</tr>
</tbody>
</table>

*Substitute CPM for IFOS for all subsequent cycles if significant Fanconi syndrome occurs. See Protocol § A-XI: 1.2 for CPM, and Mesna with CPM, doses.

**Begin each course when Plt. Ct. > 100k and ANC > 1,000.**

---

**Due Given Day Week VCR *IFOS DACT Mesna**

**DATE:**

**Comments**
(Entries must be dated)
APPENDIX X: GUIDELINES FOR TOXICITY MODIFICATIONS AND FOR SUPPORTIVE CARE

A-IX: 1.0 DOSE MODIFICATIONS FOR TOXICITIES

For intolerable or unexpected toxicity, or if a patient is removed from protocol therapy for toxicity, notify the IPPBR office (see §12.1.2 for contact information).

A-X: 1.1 Slow Blood Count Recovery

A-X: 1.1.1 Neutrophils and Platelets

The growth factors G-CSF or GM-CSF may be used at the treating physician’s discretion and must be noted on the Therapy Delivery Maps. If at the time scheduled therapy, the absolute neutrophil count (ANC) has not recovered to ≥750/µL or the platelet count < 75,000/µL, further therapy should be delayed until ANC is ≥ 750/µL and platelets ≥ 75,000/µL.

A-X: 1.1.2 Anemia

Erythropoietic growth factors (e.g. erythropoietin) may be used at the treating physician’s discretion and must be noted on the Therapy Delivery Maps.

A-X: 1.2 Fanconi Syndrome/Renal Toxicity

Elements of Fanconi Syndrome include:

1. Renal phosphorus wasting with hypophosphatemia.
2. Renal bicarbonate wasting with acidosis.
3. Renal potassium wasting with hypokalemia (< 3.0 mEq/L).
4. 1+ glycosuria with serum glucose < 150 mg/dL.
5. Proteinuria: a ratio of urine protein:urine creatinine > 0.2 occurring in the absence of significant malnutrition and acidosis due to sepsis/infection.
6. Decreased GFR.

If significant Fanconi syndrome occurs modify therapy as follows:

Cyclophosphamide replaces Ifosphamide:

Delete ifosfamide from all subsequent cycles and substitute cyclophosphamide at the dose of 700mg/m2 (23mg/kg if <3 years) x 2 days for I²VADo² courses and 700mg/m2 (23mg/kg if <3 years) x 1 day for the IVA courses with MESNA uroprotection. Dose Mesna at 60% of the daily Cyclophosphamide dose, divided into 3 doses. The first dose is given with CPM, doses 2 and 3 are given 3 and 7 hours after the start of CPM.

Future cycles of chemotherapy should include cyclophosphamide instead of ifosfamide.

A-X: 1.3 Hyperbilirubinemia

Dose modifications for patients with hyperbilirubinemia secondary to biliary obstruction due to tumor and other situations with elevated bilirubin (NOTE: elevated total bilirubin without
elevation of direct [conjugated] bilirubin is not associated with increased chemotherapy toxicity.)

<table>
<thead>
<tr>
<th>Total bilirubin</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.1 mg/dL</td>
<td>Full doses of vincristine, dactinomycin.</td>
</tr>
<tr>
<td>2.1 – 4.0 mg/dL</td>
<td>50% doses of vincristine and dactinomycin (for example, if the full vincristine dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose; if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose.</td>
</tr>
<tr>
<td>4.1 – 6.0 mg/dL</td>
<td>25% dose of vincristine, 50% dose of dactinomycin, (for example, if the full vincristine dose is 1.5 mg, then administer 0.4 mg for a 25% dose; if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose.</td>
</tr>
<tr>
<td>&gt; 6.0 mg/dL</td>
<td>Do not give vincristine; give 50% dose of dactinomycin (for example, if the full dactinomycin dose is 1.5 mg, then administer 0.7-0.8 mg for a 50% dose.</td>
</tr>
</tbody>
</table>

If the bilirubin falls prior to subsequent cycles, increase the doses as indicated above in the next cycle.

**A-X: 1.4  Veno-occlusive disease (VOD) of the liver (Hepatopathy)**

VOD graded as below and Dactinomycin dose modifications:

<table>
<thead>
<tr>
<th>Bilirubin</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 mg/dL</td>
<td>&lt; 5% of baseline of noncardiac origin</td>
<td>&gt; 6 and &lt; 20 mg/dL</td>
<td>&gt; 20 mg/dL</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>&lt; 5% of baseline of noncardiac origin</td>
<td>&gt; 5% of baseline of noncardiac origin</td>
<td>Clinical or radiologic documentation</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Clinical or radiologic documentation</td>
<td>Compromising respiratory function</td>
</tr>
<tr>
<td>Hepatic Dysfunction</td>
<td>Reversible</td>
<td>Reversible</td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>Chemotherapy modifications: Dactinomycin</td>
<td>50% dactinomycin dose for the next cycle and then resume 100% dose if tolerated.</td>
<td>Discontinue dactinomycin</td>
<td>Discontinue chemotherapy and then proceed as per moderate VOD without dactinomycin if all clinical and laboratory parameters return to normal</td>
</tr>
</tbody>
</table>

**A-X: 1.5  Cardiac Toxicity**

If prolongation of the QTc interval (> 0.44 sec), or a decrease in the shortening fraction to < 27 percent, or a decrease in the ejection fraction to < 45 percent are observed, the doxorubicin containing chemotherapy should be postponed one week, any existing malnutrition corrected and the tests repeated.

If the abnormalities persist, doxorubicin should be PERMANENTLY DISCONTINUED.

**A-X: 1.6  Neurological Toxicity**

Neurological toxicity can result from vincristine and ifosfamide.
A-X: 1.6.1 **Vincristine Neuropathy** (severe peripheral neuritis or paralytic ileus)
Vincristine should be stopped until normal bowel movements are re-established and the signs of vocal cord paralysis have disappeared, etc. Then vincristine should be restarted at 50% dosage. If problems persist or recur, the drug should be further decreased by 50% decrements. Mild to moderate constipation (lasting < 4 days) and depression of deep tendon reflexes are not indications for interrupting vincristine. If jaw pain develops, analgesics should be used.

A-X: 1.6.2 **Ifosfamide Neurotoxicity**
This is an organic brain syndrome, which ranges from mild confusion and disorientation to seizures, ataxia, and coma. It may be aggravated by impaired renal function. It usually, but does not always, resolve spontaneously, and it may or may not recur with subsequent doses.

A-X: 1.7 **Hematuria or Hemorrhagic Cystitis**
Ifosfamide dose modifications for Hematuria: Withhold ifosfamide in the presence of significant hematuria (> 50 RBCs/HPF). Restart drug after hematuria has been clear for at least 1 week at 50% dosage and increase to 100% (full dose) if tolerated. Give MESNA by continuous infusion. The total daily MESNA dose is equal to at least 60% of the daily ifosfamide dose. Urine specific gravity should be < 1.010 and bladder emptied every 2 hours x 3 after starting ifosfamide.

A-X: 2.0 **SUPPORTIVE CARE GUIDELINES**

A-X: 2.1 **Pneumocystis Carinii Prophylaxis**
Pneumocystis Carinii prophylaxis should be given per institutional standard. Alternatively, Trimethoprim/sulfamethoxazole prophylaxis should be given to all patients (TMP 5 mg/kg/day divided bid, 2 consecutive days per week). If allergic or intolerant, use pentamidine or dapsone.

A-X: 2.2 **G-CSF/GM-CSF**
G-CSF or GM-CSF can be used at the discretion of the treating physician. Note Regarding PEG-filgrastim (Neulasta): the use of PEG-filgrastim in children is still under investigation.

A-X: 2.3 **Erythropoietin**
Erythropoietin may be used with supplemental iron.

A-X: 2.4 **Blood Products Irradiation**
Blood products should be irradiated.
APPENDIX XI: DRUG INFORMATION

Dactinomycin
(Actinomycin-D, Cosmegen®) NSC #3053 (082005)

Source and Pharmacology: Dactinomycin is a member of a class of antibiotic compounds isolated from Streptomyces parvullus. Dactinomycin is composed of a planar tricyclic ring chromophore (phenoxazone) to which two identical cyclic polypeptides are attached. The compound binds to DNA by intercalation, depending on a specific interaction between the polypeptide chains and deoxyguanosine. This interaction blocks the ability of DNA to act as a template for RNA and DNA synthesis in a concentration-dependent manner. Low drug concentrations inhibit RNA synthesis more than higher drug concentrations, which block both RNA and DNA syntheses. Dactinomycin can also cause topoisomerase mediated single-strand breaks in DNA. Dactinomycin is minimally metabolized and is concentrated in nucleated red blood cells with very little diffusion into the CNS. After an I.V. bolus dactinomycin has a very short initial distribution half-life of about 1-minute but a prolonged terminal plasma half-life of about 36 hours. Dactinomycin is primarily eliminated by renal and biliary excretion. Approximately 30% of the dose is recovered in urine and feces in one week.

<table>
<thead>
<tr>
<th></th>
<th>Common: Happens to 21-100 children out of every 100</th>
<th>Occasional: Happens to 5-20 children out of every 100</th>
<th>Rare: Happens to &lt;5 children out of every 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate: Within 1-2 days of receiving drug</td>
<td>Nausea, vomiting</td>
<td>Anorexia</td>
<td>Anaphylaxis, abdominal pain, Extravasation (rare) but if occurs = local ulceration</td>
</tr>
<tr>
<td>Prompt: Within 2-3 weeks, prior next course</td>
<td>Myelosuppression , alopecia (L)</td>
<td>Diarrhea, mucositis, cheilitis, radiation recall reactions, fatigue, lethargy, malaise</td>
<td>Elevated LFT’s, hepatitis, Hepatomegaly, VOD(L), Proctitis, acne, skin eruptions Hypocalcemia, Fever, esophagitis and/or enteritis, Myalgia</td>
</tr>
<tr>
<td>Delayed: Any time later during therapy</td>
<td></td>
<td></td>
<td>Growth retardation, Pneumonitis</td>
</tr>
<tr>
<td>Late: Any time after completion of treatment</td>
<td></td>
<td></td>
<td>Secondary malignancies</td>
</tr>
</tbody>
</table>

Unknown frequency and timing: Fetal toxicities of dactinomycin have been noted in animal models. It is not known if dactinomycin is excreted into breast milk

(l) Toxicity may also occur later.

Formulation and Stability: Lyophilized powder, in vials containing 500mcg of dactinomycin, with 20mg of mannitol. Store at controlled room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from light and humidity. Reconstitute with 1.1ml of sterile H2O without preservative to give a final concentration of 500 mcg/ml (0.5 mg/ml). The resulting solution should be clear to gold colored. Preservatives may cause precipitation. Stable at room temperature 25°C (77°F), but protect from light. Use within 24 hours.

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol. Dactinomycin may be given IV push over 1-5 minutes either directly or through the tubing of a running IV infusion. Dactinomycin is compatible with dextrose or saline.
containing solutions. Significant binding of dactinomycin by cellulose ester membrane filters used in some intravenous in-line filters has been reported. Supplier: Commercially available from various manufactures. See package insert for more detailed information.

**Doxorubicin**
(Adriamycin®) NSC #123127 (01/2006)

Source and Pharmacology: An anthracycline antibiotic isolated from cultures of Streptomyces peucetius. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytotoxic activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH•. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both. Doxorubicin serum decay pattern is multiphasic. The initial distributive t½ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal t½ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 ml/min/kg and is predominately by metabolism and biliary excretion. The P450 Cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

<table>
<thead>
<tr>
<th>Common: Happens to 21-100 children out of every 100</th>
<th>Occasional: Happens to 5-20 children out of every 100</th>
<th>Rare: Happens to &lt;5 children out of every 100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immediate:</strong> Within 1-2 days of receiving drug</td>
<td>nausea, vomiting, pink or red color to urine, sweat, tears and saliva</td>
<td>Hyperuricemia, facial flushing, sclerosis of the vein</td>
</tr>
<tr>
<td><strong>Prompt:</strong> Within 2-3 weeks, prior next course</td>
<td>Myelosuppression (leucopenia, thrombocytopenia, anemia), alopecia</td>
<td>Mucositis (stomatitis and esophagitis), hepatotoxicity</td>
</tr>
<tr>
<td><strong>Delayed:</strong> Any time later during therapy</td>
<td>Cardiomyopathy (CHF occurs in 5-20% @ cumulative doses ≥450mg/m²)(L)</td>
<td>Cardiomyopathy (CHF occurs in &lt;5% @ cumulative doses ≤400mg/m²)(L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis</td>
</tr>
<tr>
<td><strong>Late:</strong> Any time after completion</td>
<td>Subclinical cardiac dysfunction</td>
<td>CHF (on long term follow up in pediatric patients)</td>
</tr>
</tbody>
</table>
Unknown Frequency and Timing: Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans.

1 Risk increases with chest radiation, exposure at a young or advanced age; (L) Toxicity may also occur later.

Formulation and Stability:
Doxorubicin is available as red-orange lyophilized powder for injection in 10mg¹, 20mg¹, 50mg¹, 150mg² vials and a preservative free 2mg/ml solution in 10mg¹, 20mg¹, 50mg¹, 75mg¹, 200mg² vials.

¹ Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben 1 mg per each 10mg of Doxorubicin to enhance dissolution.

² Multiple dose vial contains lactose, 0.9%NS, HCl to adjust pH to 3.

Aqueous Solution: Store refrigerated 2° to 8°C, (36° to 46°F). Protect from light. Retain in carton until contents are used. Powder for injection: Store unreconstituted vial at room temperature 15° to 30°C (59° to 86°F). Retain in carton until contents are used. Reconstitute with preservative-free normal saline to a final concentration of 2mg/ml. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature under normal room light (100 footcandles) and 15 days under refrigeration 2° to 8°C (36° to 46°F). Protect from exposure to sunlight.

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Administer by IV push; by IV side arm into a running infusion; or doxorubicin may be further diluted in saline or dextrose containing solutions and administered by infusion. Protect final preparation from light. Avoid extravasation.

Supplier: Commercially available from various manufactures. See package insert for more detailed information.

Ifosfamide
(Isophosphamide, Iphosphamide, Z4942, Ifex®) NSC #109724 (122004)

Source and Pharmacology: Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P-450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate, which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramid mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4g/m² to 3.8-5 g/m², respectively. At 1.6-2.4g/m²/d, 12 to 18% of the dose was excreted as unchanged drug in the urine, whereas at a 5g/m² single-dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (<10%), and the degree of such metabolism is more variable than with
cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

<table>
<thead>
<tr>
<th>Immediate: Within 1-2 days of receiving drug</th>
<th>Common: Happens to 21-100 children out of every 100</th>
<th>Occasional: Happens to 5-20 children out of every 100</th>
<th>Rare: Happens to &lt;5 children out of every 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea &amp; vomiting (acute and delayed)</td>
<td>CNS toxicity (somnolence, depressive psychosis and confusion)</td>
<td>Anorexia, diarrhea, Constipation, encephalopathy which may progress to coma (L), seizure, SIADH, Phlebitis, hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Prompt: Within 2-3 weeks, prior next course</td>
<td>Leukopenia, alopecia, Immune suppression</td>
<td>Thrombocytopenia, Anemia, Cardiac toxicities (arrhythmia, asymptomatic EKG changes), Microscopic hematuria, Metabolic acidosis</td>
<td>↑ liver enzymes, ↑ bilirubin, Hemorrhagic cystitis with macroscopic hematuria, dysuria, cystitis, and urinary frequency (&lt;5% with mesna and vigorous hydration)(L), Bladder fibrosis</td>
</tr>
<tr>
<td>Delayed: Any time later during therapy</td>
<td>Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)¹ (L)</td>
<td>Renal failure acute or chronic, RTA, Fanconi-like syndrome, Gonadal dysfunction: ovarian failure¹ (L), CHF</td>
<td></td>
</tr>
<tr>
<td>Late: Any time after completion of treatment</td>
<td>Moderate nephrotoxicity (↓ in glomerular filtration rate, renal tubular threshold for phosphate, and serum bicarbonate)</td>
<td>Secondary malignancy, Hypophosphatemic rickets</td>
<td></td>
</tr>
</tbody>
</table>

Unknown Frequency and Timing: Fetal toxicities and teratogenic effects of Ifosfamide have been noted in animals. Ifosfamide is excreted into breast milk.

¹ Dependent on dose, age, gender and degree of pubertal development at time of treatment (L) Toxicity may also occur later.

Formulation and Stability: Available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives. Reconstitute with sterile water for injection or bacteriostatic water for injection, 20ml for the 1gm vial or with 60mL for the 3gm vial to produce a final concentration of 50mg/ml ifosfamide. Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Store unreconstituted vials at room temperature 20°-25°C (68° 77°F). Protect from temperatures above 30°C (86°F). Ifosfamide may liquefy at temperatures > 35°C

Guidelines for Administration: See Treatment and Dose Modification sections of the protocol. Solutions of ifosfamide may be diluted further to concentrations of 0.6 to 20 mg/ml in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination.

Supplier: Commercially available from various manufactures. See package insert for more detailed information.

**Mesna**
(sodium 2-mercaptoethane sulfonate,UCB 3983, Mesnex®) NSC #113891 (012006)
Source and Pharmacology: Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxyifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy. After an 800mg dose the half lives for Mesna and DiMesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna tablets have an oral bioavailability of 45-79% and a urinary bioavailability which ranged from 45-79% of intravenously administered mesna. The oral bioavailability is unaffected by food. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period.

Toxicity

<table>
<thead>
<tr>
<th>Frequency and Timing</th>
<th>Common: Happens to 21-100 children out of every 100</th>
<th>Occasional: Happens to 5-20 children out of every 100</th>
<th>Rare: Happens to &lt;5 children out of every 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate: Within 1-2 days of receiving drug</td>
<td>Bad taste with oral use</td>
<td>Nausea, vomiting, stomach pain, fatigue, headache.</td>
<td>Facial flushing, fever, pain in arms, legs, and joints, rash, Transient hypotension, Tachycardia, dizziness, anxiety, Confusion, periorbital swelling, anaphylaxis, coughing.</td>
</tr>
<tr>
<td>Prompt: Within 2-3 weeks, prior next course</td>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed: Any time later during therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 All currently available products in the U.S. are preserved with benzyl alcohol. Benzyl Alcohol has been associated with death in pre-term infants weighing less than 2500 gms and receiving 99-405 mg/kg/day. Benzyl alcohol is normally oxidized rapidly to benzoic acid, conjugated with glycine in the liver, and excreted as hippuric acid. In pre-term infants, however, this metabolic pathway may not be well developed. Onset of toxic illness in these infants occurred between several days and a few weeks of age with a characteristic clinical picture that included metabolic acidosis progressing to respiratory distress and gasping respirations. Many infants also had central-nervous-system dysfunction, including convulsions and intracranial hemorrhage; hypotension leading to cardiovascular collapse was a late finding usually presaging death. [For comparison in the ICE regimen of 3000mg/m²/day of ifosfamide and a daily mesna dose of 60% of the ifosfamide dose = to 1800mg/m²/day; a child would be expected to receive 18 ml/m²/day of mesna (concentration
of 100mg/ml and 10.4mg/ml of benzyl alcohol) 187.2mg/m²/day of benzyl alcohol or 6.24mg/kg/day.]

Formulation and Stability: Available as 400mg oral tablets. Excipients include lactose, microcrystalline cellulose, calcium phosphate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone. Mesna for injection is available as 100mg/ml 10ml multidose vials which contain 0.25 mg/mL edentate disodium and sodium hydroxide for pH adjustment. Mesna Injection multidose vials also contain 10.4mg/ml of benzyl alcohol as a preservative. Store product at controlled room temperature 15-25°C (68-77ºF). Mesna is not light-sensitive, but is oxidized to DiMesna when exposed to oxygen. Mesna as benzyl alcohol-preserved vials may be stored and used for 8 days.

Mesna non-preserved ampoules are no longer provided by Bristol-Myer Squibb Company.

Guidelines for Administration: See Treatment and Dose Modifications and Supportive Care sections of the protocol. For IV administration, dilute to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Carefully expel air in syringes prepacked for use to avoid oxidation to dimesna.

Mesna may cause false positive test for urinary ketones.

Supplier: Commercially available from various manufacturers. See package insert for further information.

**Vincristine Sulfate**

(Oncovin®, VCR, LCR) NSC #67574 (032006)

Source and Pharmacology: Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

<table>
<thead>
<tr>
<th>Common: Happens to 21-100 children out of every 100</th>
<th>Occasional: Happens to 5-20 children out of every 100</th>
<th>Rare: Happens to &lt;5 children out of every 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate: Within 1-2 days of receiving drug</td>
<td>Jaw pain; headache</td>
<td>Extravasation (rare) but if occurs = local ulceration; shortness of breath and bronchospasm</td>
</tr>
<tr>
<td>Prompt: Within 2-3 weeks, prior next course</td>
<td>Alopecia, constipation,</td>
<td>Paralytic ileus; ptosis, diplopia, night blindness; hoarseness; vocal cord paralysis; SIADH, seizure; defective sweating</td>
</tr>
<tr>
<td>Delayed: Any time later during therapy</td>
<td>Loss of deep tendon reflexes</td>
<td>Difficulty walking or inability to walk; veno-occlusive disease (in combination); blindness, optic atrophy; urinary tract disorders including bladder atony, dysuria, polyuria, nocturia, urinary retention; autonomic neuropathy with postural hypotension;</td>
</tr>
</tbody>
</table>

Common:

- Happens to 21-100 children out of every 100

Occasional:

- Happens to 5-20 children out of every 100

Rare:

- Happens to <5 children out of every 100
Formulation and Stability: Vincristine is supplied in a vial each mL of which contains vincristine sulfate, 1 mg (1.08 μmol); mannitol, 100 mg; sterile water for injection; Acetic acid and sodium acetate are added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 3.5 to 5.5. This product is a sterile solution. Store refrigerated at 2-8°C or 36-46°F. Protect from light and retain in carton until time of use. Do not mix with any IV solutions other than those containing dextrose or saline.

Guidelines for Administration: See the Treatment and Dose Modifications Sections of protocol. Injection of vincristine sulfate should be accomplished within 1 minute. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion. When dispensed the container or syringe containing vincristine must be enclosed in an overwrap bearing the statement “Do not remove covering until moment of injection. Fatal if given intrathecally. For Intravenous use only.”

Supplier: Commercially available from various manufactures. See package insert for more detailed information.

**CYCLOPHOSPHAMIDE**
(Cytoxan) NSC #26271 (082006)

**Source and Pharmacology:** Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P-450 isoenzymes (CYP2B6, CYP2C9 and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramid mustard. Phosphoramid mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug.

**Toxicity:**

<table>
<thead>
<tr>
<th>Common</th>
<th>Occasional</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Happens to 21-100 children out of every 100</td>
<td>Happens to 5-20 children out of every 100</td>
<td>Happens to &lt; 5 children out of every 100</td>
</tr>
</tbody>
</table>

**Immediate:** Within 1-2 days of receiving drug
- Anorexia, nausea & vomiting (acute and delayed)
- abdominal discomfort, Diarrhea

**Prompt:** Within 2-3 weeks, prior to the next course
- Leukopenia, alopecia, Immune suppression
- Thrombocytopenia, Anemia, Hemorrhagic cystitis (L)

**Delayed:** Any time later during therapy,
- Gonadal dysfunction: azoospermia or oligospermia
- amenorrhea
- gonadal dysfunction: ovarian failure (L), Interstitial pneumonitis, pulmonary fibrosis (L)
excluding the above conditions (prolonged or permanent)\(^1\) (L)  Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis

**Late:**
Any time after completion of treatment

**Unknown Frequency and Timing:** Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast-feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.

\(^1\) Dependent on dose, age, gender and degree of pubertal development at time of treatment
\(^2\) Risk increased with chest radiation and high dose.
(L) Toxicity may also occur later.

**Formulation and Stability:** Cyclophosphamide for Injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 gm and 2 gm vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30º C (86ºF).

**Guidelines for Administration:** See Treatment and Dose Modifications sections of the protocol. Cyclophosphamide for Injection: Reconstitute with sterile water or Bacteriostatic water for injection (paraben preserved only) to a concentration of 20 mg/ml. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. If administered as undiluted drug at the 20 mg/ml concentration, reconstitute with NS only to avoid a hypotonic solution. Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

**Supplier:** Commercially available from various manufacturers. See package insert for more detailed information.
APPENDIX XII: SECONDARY AML/MDS REPORT FORM
International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

INSTRUCTIONS: Submit this form to the International Pleuropulmonary Blastoma Treatment and Biology Registry within 30 days of AML/MDS diagnosis following treatment for PPB. Submit with this form a copy of the pathology report confirming the AML/MDS diagnosis and a copy of the cytogenetic report (if available). See page 2 for mailing address. PLEASE ANSWER ALL QUESTIONS.

I. PATIENT IDENTIFICATION AND CHARACTERISTICS
Patient PPB Registry ID#: ___________________
Date of Birth (mo/day/yr): ___/___/____ Gender (please check): □ Male □ Female

II. AML/MDS DIAGNOSIS AND CHARACTERIZATION
Date of AML/MDS diagnosis: (mo/day/yr): ___/___/____
AML subtype (please check): □ M1 □ M2 □ M3 □ M4 □ M5 □ M6 □ M7
□ MDS □ Unknown □ Other (specify): ______________________
Cytogenetics performed? □ No □ Yes; please check all that apply:
□ 11q23 abnormality
□ Chromosome 5 and/or 7 abnormality
□ Other chromosome abnormality (specify): ______________________
□ Normal

III. CHEMOTHERAPY FROM INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY PROTOCOL PRIOR TO AML DIAGNOSIS
First Day Protocol Chemotherapy Taken (mo/day/yr): ___/___/____
Last Day Protocol Chemotherapy Taken (mo/day/yr): ___/___/____

<table>
<thead>
<tr>
<th>Agents Received</th>
<th>Actual Cumulative Dose Received (mg/m $^2$)</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>

Received RT? □ No □ Yes; please specify
Site: __________________________
Total Dose: ____________________

Received growth factor? □ No □ Yes; please check all that apply:
□ G-CSF □ GM-CSF □ Other (specify):

IV. CANCER THERAPY RECEIVED PRIOR TO PPB REGISTRY-SPONSORED PROTOCOL
Did the patient receive any cancer therapy (protocol or non-protocol) prior to PPB Registry protocol therapy (i.e., protocol listed in Section III)?

☐ No; if No, go to Section V. ☐ Yes

Identify agents/modalities given prior to the PPB Registry sponsored protocol therapy listed in Section III (check those which apply).

☐ Alkylators ☐ Epipodophyllotoxins ☐ Platinum ☐ Anthracyclines
☐ Other cytotoxic drugs
☐ RT; if checked, please specify:
  Site: ______________________________________________________________
  Total Dose: _______________________________________________________

V. CANCER THERAPY RECEIVED SUBSEQUENT TO LAST/CURRENT PPB REGISTRY SPONSORED PROTOCOL

Did the patient receive any cancer therapy prior to the AML/MDS diagnosis, but after completing the PPB Registry sponsored protocol therapy described in Section III?

☐ No; if No, go to Section VI. ☐ Yes

Identify agents/modalities given subsequent to the PPB Registry sponsored protocol therapy listed in Section III, but preceding the AML/MDS diagnosis (check those which apply).

☐ Alkylators ☐ Epipodophyllotoxins ☐ Platinum ☐ Anthracyclines
☐ Other cytotoxic drugs
☐ RT; if checked, please specify:
  Site: ______________________________________________________________
  Total Dose: _______________________________________________________

VI. INVESTIGATOR RESPONSIBLE FOR COMPLETING REPORT

Investigator Name (please print): ______________________________________________________________
Phone: (_____)________________________________ Fax: (_____)________________________________
Institution: ______________________________________________________________________________
Address: __________________________________________________________________________________
Investigator Signature: __________________________________ Date:______________________________

Submit this form for cases of secondary AML/MDS. The FAX # for submission of the form (including the pathology and cytogenetic reports) is ( ). Because of the poor quality of some FAX transmissions, please send a hard copy of all AML/MDS reports to the mailing address given below:

International PPB Registry
Children's Hospitals and Clinics of Minnesota
2545 Chicago Ave. S., Suite 412
Minneapolis, MN 55404 USA
### APPENDIX XIII: REPORTING SCHEDULE AND CASE REPORT FORMS

**IPPBTBR-1 TYPES I, II & III DATA AND SPECIMEN SUBMISSION SCHEDULE:**

<table>
<thead>
<tr>
<th>Required Materials</th>
<th>Send to:</th>
<th>At time of Enrollment</th>
<th>End of RT</th>
<th>End of each phase*</th>
<th>At relapse/progression/secondary malignancy</th>
<th>At time of each surgery</th>
<th>During follow-up</th>
<th>At death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment Form</td>
<td>IPPBTBRO *</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Representative Formalin-Fixed Paraffin Blocks of Tumor Material (A)</td>
<td>IPPBTBRO</td>
<td>X (A)</td>
<td></td>
<td></td>
<td></td>
<td>X (A)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology Report</td>
<td>IPPBTBRO</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tumor Biology Checklist Form</td>
<td>IPPBTBRO</td>
<td>X</td>
<td></td>
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<tr>
<td>Surgery Reporting Form</td>
<td>IPPBTBRO</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Pre-Existing Cyst Form</td>
<td>IPPBTBRO</td>
<td>X</td>
<td></td>
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<td></td>
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<tr>
<td>End of Phase/ Course Report and Completed Roadmap*</td>
<td>IPPB TBR O</td>
<td>X</td>
<td></td>
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<tr>
<td>Imaging Reports and Electronic Digital Images</td>
<td>IPPB TBR O</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>RT Course Form AND RT Treatment Summary*</td>
<td>IPPB TBR O</td>
<td>X</td>
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<tr>
<td>Follow-Up Form</td>
<td>IPPB TBR O</td>
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<td></td>
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<td>X (B)</td>
<td>X (C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse/ Progression/ SMN Form</td>
<td>IPPB TBR O</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary AML/MDS Report Form**</td>
<td>IPPB TBR O</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death Registration Form</td>
<td>IPPB TBR O</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy Report</td>
<td>IPPB TBR O</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* INTERNATIONAL PLEUROPULMONARY BLASTOMA TREATMENT AND BIOLOGY REGISTRY OFFICE (MINNEAPOLIS, MN)
**REQUIRED IF SECONDARY MALIGNANCY IS SPECIFICALLY AML/MDS
* REQUIRED ONLY FOR PATIENTS TREATED PER REGISTRY TREATMENT RECOMMENDATIONS

(A) If blocks absolutely cannot be sent, then send: (a) 1 H&E section of all available blocks, and (b) 10 unstained sections (on plus-charged, polarized slides) for immunoperoxidase studies from 2 representative blocks, and (3) 2 H&E slides from the same blocks. See protocol Appendix V

(B) Within 1 year of the end of Treatment and Biology Registry VAC (for T-I) or IVADo (for T-II & III) regimen guideline therapy, then within 1 year of completion of last form.

(C) To cover period from last follow-up form submitted to date of death.
# IPPBTBR-1: Eligibility Worksheet

<table>
<thead>
<tr>
<th>Institution:</th>
<th>Patient Name:</th>
</tr>
</thead>
</table>

- **Informed consent signed?**
  - [ ] 1= Yes
  - [ ☐ ] 2= No, Ineligible

- **Date consent (and assent, if required) signed?**
  - [ ][ ][ ] / [ ][ ] / [ ][ ][ ][ ]
  - Month Day Year

- **Patient is less than 21 years of age?**
  - [ ] 1= Yes
  - [ ☐ ] 2= No, Ineligible

- **Patient has newly-diagnosed Type I, II or III pleuropulmonary blastoma (PPB)? OR**
  - [ ] 1= Yes
  - [ ☐ ] 2= No, Ineligible

- **Patient has recurrent PPB?**
  - [ ] 1= Yes
  - [ ☐ ] 2= No

- **Female patients only: Patient is of childbearing age and pregnancy test is negative?**
  - [ ] 1= Yes
  - [ ☐ ] 2= No, Ineligible
  - [ ☐ ] 3= N/A. Patient is male, or is female but not of childbearing age

- **Has patient been informed of the PPB Genetic study?**
  - [ ] 1= Yes
  - [ ☐ ] 2= No (if not, please refer them to the study website, [http://www.ppbgeneticstudy.org/](http://www.ppbgeneticstudy.org/))

---

Fax this completed form to the International PPB Treatment and Biology Registry office, 612-813-7108.

For questions, please contact the office at 612-813-7115.
Patient Questions:

Are there any other major illnesses in the patient?: __________

Has this child ever had a chest x-ray or chest CT prior to the current situation?: ______

Has this child ever had a pneumothorax?: ______

Has this child had any lung cysts diagnosed prior to PPB?: __________

Has this child had any kidney cysts?: ______ (cystic nephroma or undiagnosed renal cysts)

Has this child had any thyroid nodules/surgery?: ______

Does this child have birth defects/syndromes/dysplasias (such as VACTERL, Fragile X, etc, etc)?: ______

If you answered YES to any of the above questions, please provide details below:


Family Questions: Has any brother, sister, parent, relative had any of the following:

Pneumothorax?: ________

Lung cysts?: ________

Kidney cysts?: ________ (esp. cystic nephroma)

Thyroid nodules or tumors?: ________

Ovarian Tumors; testicular tumors?: ________ (esp. Sertoli-Leydig ovarian tumors; testicular seminomas, ovarian dygerminomas)

Childhood Cancers?: ________ (any childhood cancer)

If you answered YES to any of the above questions, please provide details below:


Has this child’s mother or father had previous marriages?

Are there any “half-siblings” of the patient?: ______

Are there any of the above findings in any half-siblings?: ______ If YES, please provide details above.

* The questions in this survey emphasize medical conditions found in the PPB Family Tumor Susceptibility Syndrome
IPPBTBR-1 TYPES II & III TREATMENT END-OF-PHASE/COURSE REPORT FORM

Phase #: ___ Course: ___

Phase 1, Course 1 = (weeks 0-2)
Phase 1, Course 2 = (weeks 3-12)
Phase 2, Course 1 = (weeks 12-24)
Phase 3, Course 1 = (weeks 24-42)

Number of days hospitalized: ___ ___ ___ Number of hospital admissions: ___ ___ ___
Height: ___ ___ ___ cm Weight: ___ ___ . ___ kg BSA: ___ . ___ ___ m²

Date course began: ___ / ___ / ___
Date course ended: ___ / ___ / ___

Total Dose for this Course:
Ifosfamide: ___ ___ . ___ ___ mg
Vincristine: ___ ___ . ___ ___ mg
Actinomycin D: ___ ___ . ___ ___ mg
Cyclophosphamide: ___ ___ ___ ___ ___ . ___ ___ mg
Doxorubicin: ___ ___ . ___ ___ mg
Mesna: ___ ___ . ___ ___ mg

Did the patient have surgery during this course? (1= Yes; 2= No): ___
If yes, Please complete the IPPBPS Surgery Reporting Form.
IPPBTBR-1 TYPES II & III TREATMENT END-OF-PHASE/COURSE REPORT FORM

Phase #: ___ Course: ___

End-of-Course Overall Objective Response Prior to Surgery: For all patients prior to surgery. (Leave blank if no surgery was performed. Response is always recorded in comparison to the tumor size at diagnosis, not at the last evaluation.)

Response: 
1 = Complete response/remission (CR): Disease free, all sites
2 = Partial response/remission (PR): 50% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions for 4 weeks, no new lesions
3 = No response/remission (NR) or stable disease (SD): <50% decrease, and no new lesions
4 = Progressive disease (PD): 25% increase and/or the appearance of new lesions, OR Relapse/recurrence (R): Appearance of new lesions or reappearance of old lesions for patients in CR.
0 = No evaluation performed

Date of evaluation: ___/___/___

End-of-Course Overall Objective Response: For all patients (MUST BE COMPLETED). ** (Please record overall clinical response even if imaging was not performed. Response is always recorded in comparison to the tumor size at diagnosis, not at the last evaluation.)

Response: 
1 = Complete response/remission (CR): Disease free, all sites
2 = Partial response/remission (PR): 50% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions for 4 weeks, no new lesions
3 = No response/remission (NR) or stable disease (SD): <50% decrease, and no new lesions
4 = Progressive disease (PD): 25% increase and/or the appearance of new lesions, OR Relapse/recurrence (R): Appearance of new lesions or reappearance of old lesions for patients in CR.
0 = No evaluation performed

**NOTE: For patients who have had surgery this is the response following surgery.

Date of evaluation: ___/___/___

Therapy Administration:

Was therapy administered as per the Treatment and Biology Registry IVADo regimen guideline, including specified modifications for toxicity? 
(1= Yes; 2= No): ___

(NOTE: Patients terminating the Treatment and Biology Registry IVADo regimen guideline for relapse/progression, or death, are considered to have followed Registry IVADo regimen guideline?)

If no, What was the nature of the difference from the Treatment and Biology Registry IVADo regimen guideline?: 
1 = Deviation from the Treatment and Biology Registry IVADo regimen guideline, but Registry-suggested therapy will generally be followed henceforth
2 = Abandonment of the Treatment and Biology Registry IVADo regimen guideline therapy-no further attempt to follow Registry-suggested therapy
3 = N/A, patient has completed the Treatment and Biology Registry IVADo regimen per guidelines.
IPPBTBR-1  TYPES II & III TREATMENT
END-OF-PHASE/COURSE REPORT FORM

Phase #:  |  Course:  |

Off Therapy:

Was the patient taken off the Treatment and Biology Registry IVADO regimen guideline this course (including patients completing Registry-suggested therapy)?:  (1= Yes; 2= No):  

If yes, reason off the Treatment and Biology Registry IVADO regimen guideline this course:  

00 = No evaluation performed.
02 = Other physician discretion
04 = Parent/patient discretion
06 = Completed Registry-suggested therapy
08 = Unable to contact patient (lost)
10 = Death

Form completed by:

Name: _________________________  : ___________________________  / |__|__| / |__|__|__|__|
(Please print)     (Signature)  month  day  year

IPPBTBR-1  Page 3 of 3  Sept 2009
IPPBTBR-1
SURGICAL REPORTING FORM

To be submitted for any surgery AFTER beginning treatment.

Time Surgery performed: []
1 = During Phase 1, Course 1 (Types II and III only)
2 = During Phase 1, Course 2 (Types II and III only)
3 = During Phase 2, Course 1 (Types II and III only)
4 = During Phase 3, Course 1 (Types II and III only)
5 = Other

Date of Surgery: [__] / [__] / [__] / [__] / [__]
month day year

Pre-operative Status of primary site (clinical): []
1 = Complete Response (CR)
2 = Partial Response (PR)
3 = No Response (NR)
4 = Increasing Disease (INC)
9 = Unknown (UNK)

Surgical Procedure: []
1 = Lobectomy
2 = Cystectomy
3 = Wedge/segment
4 = Pneumonectomy
5 = Tumorectomy
6 = Biopsy*
7 = Other, non chest site. Specify: ________________________________________

Operative Site: []
1 = Visceral Pleura
2 = Parietal Pleura
3 = Chest Wall/Rib Cage
4 = Diaphragm
5 = Mediastinum
6 = Pericardium
7 = Major Vessels Surrounded
8 = Other, non chest site. Specify: ________________________________________

Degree of Resection: []
1 = Biopsy*
2 = Subtotal
3 = En Bloc
4 = Most/known residual
5 = Gross Total
6 = Piecemeal
7 = Other. Specify: _____________________________________________

*If Surgery to Primary Was Biopsy only:

Type of biopsy -
Open or closed: []
1 = Open; 2 = Closed; 9 = N/A
Needle or Incisional: []
1 = Needle; 2 = Incisional; 9 = N/A
Fine needle biopsy: []
1 = Yes; 2 = No; 9 = N/A

Reason for Biopsy are (check all that apply):

[] Clinically Unresectable [] Distant metastases
[] Initial Rx. Plan [] Other, specify: ____________________________
IPPBTBR-1   Treatment = IVADO
SURGICAL REPORTING FORM

Known Spill/Rupture?  □ 1 = Yes; 2 = No
Nodes Involved?     □ 1 = Yes; 2 = No
Empyema?            □ 1 = Yes; 2 = No

Was this Surgery Before Neo-Adjuvant Chemotherapy? □ 1= Yes; 2= No
Was there Vascular Invasion? □ 1= Yes; 2= No

What is the status of the patient now that this surgical procedure has been completed? □
1= Complete Response (CR)
2= Partial Response (PR)
3= No Response (NR)
4= Increasing Disease (INC)
9= Unknown (UNK)

List Other Findings or Procedures of Importance, i.e., Intestinal Resection, Application of Interstitial Irradiation, etc.:
_____________________________________________________________________________________
_____________________________________________________________________________

Form completed by:
Name: ____________________________  ____________________________  □□□/□□□/□□□□□□□□
(Please print)  (Signature)  month  day  year

Fax this completed form, along with your institution’s pathology report, to the International PPB Treatment and Biology Registry office, 612-813-7108.
For questions, please contact the office at 612-813-7115
Were preserved pathology materials sent to the IPPBTBR for Tumor Central Review?

|   | 1= Yes; 2= No |

If no, Reason not sent: ___

1= Biopsy/surgery at outside hospital
2= No excess tissue available for IRS biology studies
3= RMS not suspected at time of surgery
4= Pathology unaware of protocol requirement
5= Patient/parent refusal
6= Oversight
7= Reason not reported
9= Other,
Specify: ____________________________

Was fresh and/or frozen tissue and other Biologic Materials sent to the IPPBTBR for Biologic Studies?

|   | 1= Yes; 2= No |

If no, Reason not sent: ___

1= Biopsy/surgery at outside hospital
2= No excess tissue available for IRS biology studies
3= RMS not suspected at time of surgery
4= Pathology unaware of protocol requirement
5= Patient/parent refusal
6= Oversight
7= Reason not reported
9= Other,
Specify: ____________________________
RADIATION COURSE FORM

Start Date of Radiation Therapy: ___/___/____

End Date of Radiation Therapy: ___/___/____

Description of Radiation Course: ___

Radiation Modality: ___

Course description:
Preferred course description = total cGy, # of fractions, field description, elapsed days [= “duration”] (e.g.: 400 cGy in 20 fx to whole brain in 26 days).

Site Location for Radiation Therapy: ________________________________

Primary Treating Radiation Oncologist: ________________________________

Form completed by:

Name: ___________________________ : _____________________________ ___/___/____
(Please print) (Signature) month day year

Fax this completed form, along with the Radiation Therapy Summary Report, to the International PPB Treatment and Biology Registry office, 612-813-7108.

For questions, please contact the office at 612-813-7115.
FOLLOW UP FORM

Time period covered by this form:
From:     /    /          
month day year
To:     /    /          
month day year

Current Known Status:  
1= No Evidence of Disease
2= Dead of Disease
3= Alive with Disease
4= In Primary Treatment
5= In Recurrence/Metastatic Treatment
6= Lost to Follow-up

[] Did this patient relapse/progress during this reporting period?
1= Yes; 2= No
If yes, Complete Relapse/Progression/Second Malignant Neoplasm Form

[] Was this patient diagnosed with a second malignancy during this reporting period?
1= Yes; 2= No
If yes, Complete Relapse/Progression/Second Malignant Neoplasm Form

[] Did the patient die during this reporting period?
1= Yes; 2= No
If yes, Complete Relapse/Progression/Second Malignant Neoplasm Form

[] Is this patient now lost to follow-up?
1= Yes; 2= No
If yes, complete the following:

[] Number of attempts to contact patient

Methods tried, check all that apply:
[] Phone
[] Letter
[] Family doctor
[] Other, Specify: _______________________________________

Form completed by:
Name: __________________________ : ______________________________ 
(Please print) (Signature) month day year

IPPBTBR-1 Page 1 of 1 Sept 2009
IPPBTBR-1  Treatment = IVADo

RELAPSE/PROGRESSION/SECOND MALIGNANT NEOPLASM FORM

Date of Relapse/Progression/Second Malignant Neoplasm:  __/__/____

How was Relapse/Progression/Second Malignant Neoplasm Diagnosed? Check all that apply:

[ ] Simple X-Ray  [ ] Biopsy
[ ] XR-CT  [ ] Surgery
[ ] MRI  [ ] Physical Exam
[ ] XR – Nuc. Scan  [ ] Other. Explain ______________________________

If Relapse/Progression:  1= Yes; 2= No

Local recurrence:  [ ]
Regional nodes:  [ ]
Metastases:  [ ]
If yes, New?:  [ ]

Surgically proven:  [ ]  (If yes, Send OP/Path or BM Reports, and complete the IPPBPS Surgery Reporting Form)

Sites: ______________________________________________________________________

If Second Malignant Neoplasm:

Type: ______________________________________________________________________

Send OP/Path or BM Reports and AML/MDS Report if applicable.)

Sites: ______________________________________________________________________

Notes:

- If patient has a Relapse/Progression on the SAME date as a Second Malignant Neoplasm use one form for all data.

- If patient has a Relapse/Progression on one date and a Second Malignant Neoplasm on another date complete two forms -- one for the Relapse/Progression and another for the Second Malignant Neoplasm.

Form completed by:

Name: ___________________________ : ___________________________  __/__/____
(Please print) (Signature)  month  day  year

IPPBTBR-1  Page 1 of 1  Sept 2009
## DEATH REGISTRATION FORM

**IPPBTBR-1 Treatment = IVADo**

### Date of Death:
- Month: __
- Day: ___
- Year: ___

### Was autopsy done?
- 1 = Yes
- 2 = No
- 9 = Unknown

### CAUSE(S) OF DEATH:

*Was this factor a significant* contributory factor in death? (*A factor is "significant" if it played an integral part in the patient’s death*)

**Codes:**
- 1 = Yes
- 2 = No
- 9 = Unknown

<table>
<thead>
<tr>
<th>Cause</th>
<th>Site</th>
<th>Other</th>
<th>Give details:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Progressive disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. GVHD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Operative complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Unrelated to original</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnosis &amp; treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(e.g.; drowning)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Did the patient die within 3 months of the end of IPPBPS protocol therapy or while on IPPBPS protocol therapy? (1 = Yes; 2 = No)
- If yes, how were the side effects of protocol therapy related to the patient's death?
  - 1 = Not related
  - 2** = Minor contribution to death
  - 3** = Major contribution to death
  - 4** = Exclusive cause of death

**If 2, 3 or 4, Explain the relationship:**

- If you had to pick one, which of the above (1-8) was the main reason the patient died?

---

**Form completed by:**

*Name:* __________________________

*Registry ID Number: ____________________________

*Institution Name: ____________________________

*Signature:* ____________________________

*Month: ___  Day: ___  Year: ___**

**IPPBTBR-1 Page 1 of 1  Sept 2009**
IPPBTBR-1  Treatment = IVADo
PRE EXISTING CYST FORM

Date Cyst(s) First Noted:  | | | / | | | / | | | |
month  day  year

When cysts were first noted, did the patient have a pneumothorax? | 1= Yes; 2= No; 9= Unknown

Number of Cysts:  | | |

Location of lung cyst(s): Check all that apply:

- [ ] Right
- [ ] Upper
- [ ] Mid
- [ ] Lower
- [ ] Pleura
- [ ] Diaphragm
- [ ] Lingula
- [ ] Unspecified

Size of Cysts:  | | . | | . | | cm x | | . | | . | | cm  Cyst Location: ____________________
| | . | | . | | cm x | | . | | . | | cm  Cyst Location: ____________________
| | . | | . | | cm x | | . | | . | | cm  Cyst Location: ____________________
| | . | | . | | cm x | | . | | . | | cm  Cyst Location: ____________________
| | . | | . | | cm x | | . | | . | | cm  Cyst Location: ____________________

Cyst Description: | 1= unilocular; 2= multilocular; 9= Unknown

Method of Measurement: | 1= MRI  5= Radionuclide Scan
| 2= CT Scan  6= Physical Exam
| 3= X-ray  9= Other (specify: ________________)
| 4= Ultrasound

Form completed by:
Name: _____________________________: _____________________________ | | | / | | | / | | | |
(Please print) (Signature)  month  day  year

IPPBTBR-1  Page 1 of 1  Sept 2009
IPPBTBR-1  
Treatment = IVADo

DIAGNOSTIC SPECIMEN TRANSMITTAL FORM

See protocol sections Appendix V.

<table>
<thead>
<tr>
<th>Date of Surgery:</th>
<th>Surgical Pathology #:</th>
</tr>
</thead>
<tbody>
<tr>
<td>__</td>
<td>__ / __ / __</td>
</tr>
</tbody>
</table>

month     day            year

<table>
<thead>
<tr>
<th>Referring Pathologist</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name of Referring Institution</th>
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<table>
<thead>
<tr>
<th>Referring Institution Address</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>City</th>
<th>State</th>
<th>Zip/Postal Code</th>
</tr>
</thead>
</table>

<table>
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<tr>
<th>Country</th>
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</table>

<table>
<thead>
<tr>
<th>Telephone #</th>
<th>Fax #</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Contact Person’s Email</th>
</tr>
</thead>
</table>

Include the following with your submission:

- A complete set of hematoxylin and eosin-stained slides
- A complete pathology report
- One representative paraffin block or 15 unstained sections
- Your contact information including phone number, fax, and e-mail address
- This form, filled out in its entirety

Comments/Instructions: ____________________________________________________________

Shipping

Arrangements should be made for Federal Express pick-up according to the usual institutional procedure. Call ahead (612-813-7115) to receive a Federal Express account number for your shipment.

Specimens should be shipped to:

International Pleuropulmonary Blastoma Registry
Children’s Hospitals and Clinics of Minnesota
2545 Chicago Ave. S.
Suite 412
Minneapolis, MN 55404   USA
Telephone: 612-813-7115
Email: gretchen.williams@childrensmin.org

FOR INTERNATIONAL SHIPMENTS:

Please label outside of the package with the following:
“The package contains preserved, non-infectious human tissue on glass slides or in paraffin wax for medical diagnosis purposes.”
REFERENCES

CHCMN IRB DOCUMENTATION FOR AMENDMENTS AND APPROVALS
To: Yoav Messinger, MD  
Hematology/ Oncology

From: Debra McKeenan, MS  
IRB Administrator

Date: September 14, 2011

Re: IRB# 0909-062 Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

The Institutional Review Board (IRB) reviewed your progress report at its meeting on September 14, 2011 and has APPROVED renewal of the referenced study. Your study will be reviewed by the IRB again in 12 months. The approval for this study will expire September 13, 2012.

Reminder: Please note the approval date (September 14, 2011) on the consent forms if applicable.

Please be reminded to inform the IRB of any protocol changes, unanticipated problems, adverse events or study closure in the interim.

We wish you continued success with your research.

Cc: Gretchen Williams, BS, CCRP
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

I. IRB Number: 0000-1234
   Principal Investigator: Yoav Massinger, MD
   Study Title: International Pleuropulmonary Blasatoma (PPB) Treatment and Biology Ronisky

II. Description of the amendment.
   A. Briefly describe the proposed amendment.

   Due to the fact that clinical testing for the DICER1 gene is now available, we are eliminating the request for "research only" DICER1 specimen procurement in this protocol.
   We are making administrative changes by including all appendices separately.

   B. Attach any supplemental materials (e.g., sponsor’s copy of the amendment, safety data, revised consent forms, etc.)

      See attached.

III. Describe the rationale for this amendment.

   Prior study included research DICER1 gene testing and the patients were not provided with results. It would not be ethical to ask subjects to consent to such a study when clinical testing is now available.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

   We believe that this amendment will actually decrease risks.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

   Yes, the consent form should be changed to indicate that research only genetics specimen collection is no longer part of the study. Other specimens will still be collected.

Investigator’s Signature: ____________________________ Date: 7/1/11

fاسمهد.doc07-09
To: Yoav Messinger, M.D.
Hematology/Oncology

From: Debra McKeen, MS
IRB Administrator

Date: July 13, 2011

Re: Amendment to IRB#0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment dated 7/11/11 is APPROVED as submitted, by expedited review procedures.

The amendment eliminates specimen procurement for DICER1 gene testing from the study, because DICER1 gene testing is now available clinically. Appropriate changes have been made to the protocol and consent.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

I. IRB Number: 0909-082
Principal Investigator: Yossi Messinger, MD
Study Title: International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment.
A. Briefly describe the proposed amendment.

This proposal requests an additional Registry consent form which will allow parents to directly enroll their child in the Registry.

Not having these consent forms in our initial application was an error on the part of the study committee. Both the IRB application (section 5) and the protocol (section 3.1) state that individuals may directly consent. Also, the original PPB Registry study protocol (IRB #98107) allows individual enrollment.

B. Attach any supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)

The new consent forms are attached. These will complement existing consents.

III. Describe the rationale for this amendment.

Realizing that not every physician will open the study at his or her institution, we seek to allow individuals being treated outside of Children's Hospitals and Clinics of Minnesota to enroll directly in the PPB Treatment and Biology Registry.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

This amendment will not affect the overall risks of the study.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

Yes, an additional consent form is required. See sections II and III above.

Investigator's Signature: Y. Messinger  Date: 8/16/11

AMEND.cc/07-09
INTEROFFICE MEMO

Children's Hospitals and Clinics of Minnesota

To: Yoav Messinger, MD
   Hematology/Oncology

From: Debra McKeehan, MS
       IRB Administrator

Date: August 29, 2011

Re: Amendment to IRB#0909-082 Pleuropulmonary Blasomata (PPB) Treatment and Biology Registry

Your amendment request, dated 8/16/11, was reviewed by expedited review and is APPROVED as submitted.

The amendment includes:
   1) Additional Registry consent, assent, Authorization for Release of Information, and HIPAA Authorization forms, which will allow parents to directly enroll children with Type I and Types II and III PPB in the Registry.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

cc: Gretchen Williams
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

IRB Contact Name: 
Gretchen Williams, BS, CCRP 
e-mail: Gretchen.williams@childrens.mn.org 
Mailstop: 17-412

I. IRB Number: 0909-062
   Principal Investigator: Yoav Messinger, MD
   Study Title: International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment.
   A. Briefly describe the proposed amendment.

   We would like to be able to use best available method to send consent forms and receive signed consent forms. We request that this include mail (postal service), scanned documents and fax.

   B. Attach any supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)

   The consent form is unchanged. The amendment refers to the way in which the consent is received and sent by the family.

III. Describe the rationale for this amendment.

   As technology changes so do the options by which families or physicians can return completed Registry consents forms. To serve them better we would like to give them the options to mail, fax, or scan the signed consent documents to the PPB Registry.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

   No, it does not alter risks. The consent form which is sent to the family contains no identifying information when it is sent out by us. There is identifying information on it when it is returned by the family but they always have the option to send by the mechanism they prefer (mail, scanned document or fax).

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

   No change to consent form is needed.

Investigator's Signature: [Signature] Date: 6/11/12
To: Yoav Messinger, M.D.
Hematology/Oncology

From: Debra McKeeshen, MS
IRB Administrator

Date: June 13, 2012

Re: Amendment to IRB#0909-082 International Pleuropulmonary
Blastomas (PPB) Treatment and Biology Registry and IRB# 98107 The
International Pleuropulmonary Blastoma (PPB) Registry

Your amendment dated 6/11/12 is APPROVED as submitted, by expedited review
procedures.

The amendment requested permission to send and receive consent forms using mail,
scanned documents, or fax methods.

Please be reminded that you are required to inform this office of any changes beyond
this amendment. You must notify this office of any additional risks, unanticipated
problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

IRB Contact Name: 
Gretchen Williams, BS, CORP

E-mail: Gretchen.williams@childrensminn.org

Mailstop: 17-412

I. IRB Number:
0509-062

Principal Investigator:
Yoav Mesinger, MD

Study Title:
International Pneumopulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment.

A. Briefly describe the proposed amendment.

We would like to add the following physicians to the Registry Committee:
- Dr. Douglas Stewart. He will provide statistical analysis and support
- Dr. Philip Rosenberg. He will provide statistical analysis and support
- Dr. Douglas Minniti. He will provide surgical guidance

B. Attach any supplemental materials (e.g., sponsor’s copy of the amendment, safety data, revised consent forms, etc.)

Not applicable

III. Describe the rationale for this amendment.

These physicians will bring their specialty skills to the PPB Registry, allowing us to analyze existing and future data and thereby offer improvements in the diagnosis and treatment of PPB.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

Adding these physicians will in no way affect overall risks of the study.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

The consent form does not need to be changed.

Investigator’s Signature: [Signature]

Date: 4/1/12
To: Yoav Massinger, M.D.
Hematology/Oncology

From: Debra McKeel, MS
IRB Administrator

Date: June 12, 2012

Re: Amendment to IRB#0909-382 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment dated 6/11/12 is APPROVED as submitted, by expedited review procedures.

The amendment requested the addition of the following physicians to the Registry Committee:
- Dr. Douglas Stewart
- Dr. Philip Rosenberg
- Dr. Douglas Minnati

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams
Memo

Date: August 22, 2012
To: Yoav Messinger, MD
From: Debra McKeenen, MS

IRB Administrator

Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

The Institutional Review Board (IRB) reviewed your progress report at its meeting on August 22, 2012 and has APPROVED renewal of the referenced study. The approval for this study will expire August 21, 2013.

Please note an IRB re-approval date of August 22, 2012 on the consent and assent forms.

Please be reminded to inform the IRB of any protocol changes, unanticipated problems, adverse events, or study closure in the interim.

We wish you continued success with your research.

Cc: Jennifer Lee
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

IRB Contact Name: Gretchen Williams, BS, CCRP
e-mail: Gretchen.williams@childrensmn.org Mailstop: 17-412

<table>
<thead>
<tr>
<th>IRB Number:</th>
<th>0909-082</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Investigator:</td>
<td>Yoav Messinger, MD</td>
</tr>
<tr>
<td>Study Title:</td>
<td>International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry</td>
</tr>
</tbody>
</table>

II. Description of the amendment.
A. Briefly describe the proposed amendment.

We would like to add the following physician to the Registry Committee:
- Dr. Brad Feltis, M.D. PhD
  Pediatric Surgical Associates
  2530 Chicago Ave S Suite 550
  Minneapolis, MN 55404

  Dr. Feltis will provide surgical guidance to the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

B. Attach any supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)
Not applicable

III. Describe the rationale for this amendment.

Dr. Feltis will bring his specialty skills to the PPB Registry, allowing us to analyze existing and future data and thereby offer improvements in the diagnosis and treatment of PPB.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

Adding Dr. Feltis to the Registry Committee will in no way affect overall risks of the study.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

The consent form does not need to be changed.

Investigator's Signature: ___________________________ Date: ___________________
Memo

Date: November 5, 2012
To: Yoav Messinger, MD
From: Debra McKeeken, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 10/24/12, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:

• The addition of Brad Feltis, MD, PhD to the Registry Committee.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

IRB Contact Name:   Gretchen Williams, BS, CCORP  e-mail: Gretchen.williams@childrensny.org  Mailstop: 17-412

I. IRB Number: 0909-082

Principal Investigator: Yoav Messinger, MD

Study Title: The International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment.

A. Briefly describe the proposed amendment.

The International PPB Treatment and Biology Registry (IPPR) would like permission to send a letter to IPPB study participants diagnosed also with an ovarian or testicular tumor. The letter will inform them/their child of another registry, The International Ovarian and Testicular Stromal Tumor (OTST) Registry. The OTST Registry seeks to specifically learn more about ovarian and testicular tumors in families affected by PPB and/or other PPB-associated diseases.

B. Attach any supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)

Letter template attached.

III. Describe the rationale for this amendment.

Over the years the IPPB Registry has shown a link between PPB and ovarian or testicular tumors. The IPPBR captures only brief details regarding these second malignancies. The OTST Registry would like to research that link further with the hopes of finding the correlation.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

We do not believe this change has any overall risk.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

We do not feel the consent needs to be changed. The consents require subjects to "opt in" for future contact. Families who request no future contact will not receive this letter.

Investigator's Signature: [Signature]  Date: 10/8/12.
Memo

Date: October 12, 2012
To: Yoav Messinger, MD
From: Debra McKeen, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment request, dated 10/8/12, was reviewed and approved by expedited review by the Institutional Review Board.

Included in this approval:

- Permission to send a letter to inform subjects, diagnosed with ovarian or testicular tumors, of the Ovarian and Testicular Stromal Cell Tumor Registry, if they have indicated that they wanted to be contacted.
- Approval of sample letter, as revised.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. No handwritten forms will be accepted.

<table>
<thead>
<tr>
<th>Study Coordinator/IRB Liaison Name:</th>
<th>e-mail:</th>
<th>Mailstop:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gretchen Williams, BS, CCRP</td>
<td><a href="mailto:gretchen.williams@childrensmp.org">gretchen.williams@childrensmp.org</a></td>
<td>17-112</td>
</tr>
</tbody>
</table>

I. IRB Number: 0909-082
Principal Investigator: Yaey Massinger, MD
Study Title: International Pleuropulmonary Blastosomas (PPB) Treatment and Biology Registry

II. Description of the amendment.
A. Briefly describe the proposed amendment.
We would like to offer the PPB Registry Type II and III consents in Spanish for the Latino population.

B. List any attached supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)
Attached.

III. Describe the rationale for this amendment.
The PPB Registry realizes that patients enroll in this study from around the globe. While it would be too costly to translate the consents into every language, we feel it beneficial to have them available in Spanish.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.
This change does not affect the overall risks of the study. In fact, it will allow the subjects to be better informed.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.
The current consent should not be replaced. This consent will be in addition, not a replacement for it.

Investigator's Signature: [Signature]
Date: 1/22/13

Rev: sec 1/22/20-3
Memo

Date: January 29, 2013
To: Yoav Messinger, MD
From: Debra McKeehen, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 1/22/2013, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:

- Spanish versions of consents for Type II and III subjects.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
AMENDMENT REQUEST FORM

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<table>
<thead>
<tr>
<th>Study Coordinator/IRB Liaison Name:</th>
<th>e-mail:</th>
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<tbody>
<tr>
<td>Gretchen Williams, BS, CCRP</td>
<td><a href="mailto:Gretchen.williams@childrensmn.org">Gretchen.williams@childrensmn.org</a></td>
<td>17-412</td>
</tr>
</tbody>
</table>

I. IRB Number: 0909-082
Principal Investigator: Yoav Messinger, MD
Study Title: International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment.
   A. Briefly describe the proposed amendment.

   We would like to offer the PPB Registry Type I consent in Spanish for the Latino population.

   B. List any attached supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)

   Attached.

III. Describe the rationale for this amendment.

   The PPB Registry realizes that patients enroll in this study from around the globe. While it would be too costly to translate the consents into every language, we feel it beneficial to have them available in Spanish. (Originally we did not think we had funding in 2013 to translate the Types II and III consent, and the Type I consent, which is why we didn't submit this as one amendment.)

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

   This change does not affect the overall risks of the study. In fact, it will allow the subjects to be better informed.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

   The current consent should not be replaced. This consent will be in addition, not a replacement, for it.

Investigator's Signature: ___________________________ Date: _____________________

Revised 1/2/2013
Date: March 25, 2013
To: Yoav Messinger, MD
From: Debra McKeenan, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 3/14/2013, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:

- Spanish version of consent for Type I subjects.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
Memo

Date: August 14, 2013
To: Yoav Messinger, MD
From: Debra McKeheen, MS (IRB)-IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

The Institutional Review Board (IRB) reviewed your progress report at its meeting on August 14, 2013 and has APPROVED renewal of the referenced study. The approval for this study will expire August 13, 2014.

Please note an IRB re-approval date of 8/14/13 on the consent and assent forms.

Please be reminded to inform the IRB of any protocol changes, unanticipated problems, adverse events, or study closure in the interim.

We wish you continued success with your research.

Cc: Anne Harris
    Gretchen Williams
    Jennifer Lee
Memo

Date: January 3, 2014
To: Yoav Messinger, MD
From: Debra McKeenen, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 12/16/13, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:

- Addition of Dr. Jacob Langer to the Registry Committee

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

Study Coordinator:
IRB Liaison Name: Gretchen Williams, BS, CCRP

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<tr>
<td><a href="mailto:Gretchen.williams@children.mn.org">Gretchen.williams@children.mn.org</a></td>
<td>17-412</td>
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I. IRB Number: 0909-582
   Principal Investigator: Yeaz Messinger, MD
   Study Title: International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment
   A. Briefly describe the proposed amendment.

   We are requesting the following physician be added to the Registry Committee:
   Jacob Langer, M.D.
   Division of General Surgery
   The Hospital for Sick Children
   555 University Ave., Suite 1526
   Toronto, ON
   M5G 1X8 CANADA

   Dr. Langer will provide his expert surgical opinion to the International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

   B. List any attached supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)

   Not applicable

III. Describe the rationale for this amendment.

   Dr. Langer will bring his specialty skills to the PPB Registry, allowing us to analyze existing and future data and thereby offer improvements in the diagnosis and treatment of PPB.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

   Adding Dr. Langer to the Registry Committee will in no way affect overall risks of the study.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

   The consent form does not need to be changed.

Investigator’s Signature: [Signature]
Date: [Date]

Revised 1/2/2013
Memo

Date: January 3, 2014
To: Yoav Messinger, MD
From: Debra McKehee, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 12/16/13, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:

- Addition of Dr. Leslie Doros to the Registry Committee

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

Study Coordinator/IRB Liaison Name: Gretchen Williams, BS, CCRP
e-mail: Gretchen.williams@childrensny.org
Phone #: 17-412

I. IRB Number: 0909-052
Principal Investigator: Yoav Messinger, MD
Study Title: International Pleuropulmonary Blastosoma (PPB) Treatment and Biology Registry

II. Description of the amendment.
A. Briefly describe the proposed amendment.

We are requesting the following physician be added to the Registry Committee:

Leila Doros, MD
Children's National Medical Center
Division of Surgical Pathology
111 Michigan Ave. NW
Washington DC 20010
E-mail: LDoros@cnmc.org
Telephone: 202-476-5173

Dr. Doros was a fellow under Dr. Hill and is now a medical oncologist.

B. List any attached supplemental materials (e.g., sponsor's copy of the amendment, safety data, revised consent forms, etc.)
   Not applicable

III. Describe the rationale for this amendment.

Dr. Doros brings expert pathology, oncology, and genetic opinion to the International Pleuropulmonary Blastosoma (PPB) Treatment and Biology Registry.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.

   Adding Dr. Doros to the Registry Committee will in no way affect overall risks of the study.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.

   The consent form does not need to be changed.

Investigator's Signature: __________________________ Date: 1/2/13

Revised 1/2/2013
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. No handwritten forms will be accepted.

Study Coordinator:
IRB Liaison Name: Gretchen Williams, BS, CCAR
Phone #: 17-412
e-mail: Gretchen.williams@childrensmn.org

I. IRB Number: 0809-022
Principal Investigator: Yoav Messinger, MD
Study Title: International Pleuropulmonary Blasto (PPB) Treatment and Biology Registry

II. Description of the amendment.
   A. Briefly describe the proposed amendment:
      1) We are requesting to move the PPB-Associated Diseases portion of IRB study #8107 to this study to have all current information available in one protocol.
      2) Pathology procurement advances allow for fresh tissue to be analyzed by pathologists, just as frozen tissue and blocks. The Registry would like to add this option to the protocol.

   B. List any attached supplemental materials (e.g., sponsor’s copy of the amendment, safety data, revised consent forms, etc.):
      a) Revised protocol
      b) Consent forms for the PPB-Associated Diseases arm of this study

III. Describe the rationale for this amendment.
   1) Moving the associated diseases arm of the PPB Registry to this protocol will allow protocol #8107 to close quicker. The proposed consent will also more accurately reflect the current state of Registry work.
   2) Additional testing is now available which will help in the diagnosis and treatment of PPB.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.
   1) It will not affect the overall design of the study. Patients with conditions associated to PPB who consent to this study will continue to have their own physician(s) determined care and follow up.
   2) This will not affect the overall risks of the study. Any tumor tissue sent is leftover tissue.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.
   1) Yes, an additional consent specific to the associated diseases arm of the Registry is necessary. The Registry physicians will not offer treatment recommendations for these patients.
   2) No, specific details of how the tissue is prepared and sent is not included in the consent.

Investigator’s Signature: [Signature]
Date: [Date]

Revised 1/2/2013
Memo

Date: February 6, 2014
To: Yoav Messinger, MD
From: Debra McKeheen, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 1/24/14, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:
- Revised protocol-
  - PPB-Associated Diseases portion of IRB# 98107 added to IRB# 0909-082
  - Protocol changed to allow for fresh tissue to be analyzed by pathologists
- Additional consent added for PPF-Associated arm of this study

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

Study Coordinator/IRB Liaison Name:  
Gretchen Williams, BS, CCRP  
e-mail: Gretchen.williams@childrensminn.org  
Phone #: 5-7115

I. IRB Number: 0609-087  
Principal Investigator: Yoav Meesinger, MD  
Study Title: International Pleuropulmonary Blasatoma (PPB) Treatment and Biology Registry

II. Description of the amendment.  
A. Briefly describe the proposed amendment.  
We are asking for authorization for Anne Harris and Ann Blake to obtain informed consent for this study.

B. List any attached supplemental materials (e.g., sponsor’s copy of the amendment, safety data, revised consent forms, etc.)  
N/A.

III. Describe the rationale for this amendment.  
Because they have taken on more duties within the PPB Registry, both may be called upon to discuss the study and the Registry with families, thus they should be allowed to consent individuals.

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.  
This will not affect overall risks.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.  
The consent form does not need to be changed.

Investigator's Signature:  
Date: 2-13-14

Revised 1/2/2013
Memo

Date: February 24, 2014
To: Yoav Messinger, MD
From: Debra McKeen, MS
IRB Administrator
Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 2/13/2014, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:
  * Authorization for Anne Harris and Ann Blake to obtain informed consent from subjects.

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
IRB Continuing Review Report

Please mail completed form to:
IRB Administration, Mailstop: 40-420.
(address for submissions from outside Children's on previous Instruction Page.)

IRB Number: 0509-082

Principal Investigator: Yoos Measinger, MD

Study Title: IRB #3089-082 International Pleuropulmonary Blastoma (PPB): Treatment and biology Registry

Date of Report (MM/DD/YY): 6/17/14
Date of Expiration of IRB Approval (MM/DD/YY): 8/13/14

Individual to receive IRB Correspondence: (This is usually the Study Coordinator if there is one.)
Name: Jennifer Lee
Email: jennifer.lee@childrensmn.org
Address if off-site: 17 412

Please indicate the current status of this project (choose only one):

☐ Study completed or discontinued. We wish to close the study. STOP Do not complete this form.
Please complete IRB Study Notice of Closure/Final Report Form at Sponsor's Review Board or on StarNet: Institutional Review Board page.

☐ Study not ongoing active: Explain: 
Sign and date form and return to IRB office.

☐ Study on hold/suspended: Explain: 
Answer all questions. Remember to sign form.

☐ Recruitment complete: (study permanently closed to enrollment of new subjects). In follow-up subjects are receiving research intervention. 
Complete the rest of this form. CHANGE: NA if a question is not applicable to your study. If any questions are not applicable and tick mark box, remember to sign form.

☐ Recruitment complete (study permanently closed to enrollment of new subjects). In follow-up and subjects are NOT receiving research intervention

Data collection complete and/or data analysis only: No new subjects or no new records/data will be accessed; will be entered. We wish to keep the study open.

Preparer: Printed Name: Ann Brakke, CRA

Signature of Report Preparer;

Investigator: Printed Name: Yoos Measinger, MD

Preparer's Printed Name: 

Signature of Principal Investigator:

Date: 6/17/14

Date: 6/17/14
AMENDMENT REQUEST FORM

A complete typed form is required for IRB review. NO handwritten forms will be accepted.

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<td><a href="mailto:Gretchen.williams@childrensmn.org">Gretchen.williams@childrensmn.org</a></td>
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I. IRB Number: 0909-082
Principal Investigator: Yoav Messinger, MD
Study Title: International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

II. Description of the amendment.
A. Briefly describe the proposed amendment.
   1) We are requesting to move the PPB-Associated Diseases portion of IRB study #98107 to this study to have all current information available in one protocol.
   2) Pathology procurement advances allow for fresh tissue to be analyzed by pathologists, just as frozen tissue and blocks. The Registry would like to add this option to the protocol.

B. List any attached supplemental materials (e.g., sponsor’s copy of the amendment, safety data, revised consent forms, etc.)
   - Revised protocol
   - Consent forms for the PPB-Associated Diseases arm of this study

III. Describe the rationale for this amendment.
   1) Moving the associated diseases arm of the PPB Registry to this protocol will allow protocol 98107 to close to accrual. The proposed consents will also more accurately reflect the current scope of Registry work.
   2) Additional testing is now available which will help in the diagnosis and treatment of PPB

IV. Briefly explain your opinion as to whether or not this amendment will affect the overall risks of the study, describing in what way it does so.
   1) It will not affect the overall risks of the study. Patients with conditions associated to PPB who consent to this study will continue to have their own physician(s) determined care and follow up.
   2) This will not affect the overall risks of the study. Any tumor tissue sent is leftover tissue.

V. Describe whether or not the consent form should be changed based on this amendment. If it should be changed, please indicate in what way.
   1) Yes, an additional consent specific to the associated diseases arm of the Registry is necessary. The Registry physicians will not offer treatment recommendations for these patients.
   2) No, specific details as to how the tissue is prepared and sent is not needed in the consent.

Investigator’s Signature: [Signature]
Date: 1/2/2013

Revised 1/2/2013
Memo

Date: February 6, 2014
To: Yoav Messinger, MD
From: Debra McKeelen, MS
IRB Administrator

Subject: IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

Your amendment to the study referenced above, dated 1/24/14, was reviewed and approved by the Institutional Review Board (IRB) by expedited review.

The amendment requested approval for:

- Revised protocol-
  - PPB-Associated Diseases portion of IRB# 98107 added to IRB# 0909-082
  - Protocol changed to allow for fresh tissue to be analyzed by pathologists
- Additional consent added for PPF-Associated arm of this study

Please be reminded that you are required to inform this office of any changes beyond this amendment. You must notify this office of any additional risks, unanticipated problems, or termination of this research protocol.

We wish you continued success in your research.

Cc: Gretchen Williams, BS, CCRP
Children's Hospitals and Clinics of Minnesota-Institutional Review Board
Study Personnel Amendment Request Form- Add/Remove/Change

A completed form is required for IRB review; forms with incomplete information will be returned.
- Mail to IRB Administration, M540-420

IRB Number: 0909-082  Principal Investigator: Yoav Messinger, MD

Study Title: International Pleuropulmonary Blastoma Treatment and Biology Protocol

Send approval to: Gretchen Williams  Email address: gretchen.williams@childrensminn.org

Address, if not at Children's

Status Change  Add as study personnel

Name: Joyce Turner  Degree(s): IMS  E-Mail Address: JTurner@childrensnational.org

Institution and Department (if not Children's employee and have another affiliation)  11 Michigan Ave, NW, Washington, DC 20010

Role in the Study  Other Research Staff
Will the individual be consenting research subjects?  No
Will the individual be working with data? (indicate what kind of data)  PHH (Protected Health Information)
Will the individual have contact with research subjects?  Yes

Describe Research Activities on this Principal Investigator's Signature:
Research Study  Involved with the enrollment of families into the DORI study, collection of individual and family medical histories via questionnaire with medical record confirmation, construction of multi-generation pedigrees, and will (Date)

IRB Reviewer Section (IRB Office Use Only)

☑ Approved: I have reviewed this request, the protocol and the consent form (if applicable), and I confirm the above referenced amendment meets the applicable criteria for expedited review process by the Institutional Review Board

☐ Does not meet the criteria for expedited review and requires full IRB review (Changes in PI, for studies originally reviewed by the full board, will be placed on the IRB agenda for the next available meeting.)

☐ Meets the criteria, however, the reviewer is recommending full IRB review

IRB Reviewer's Signature: Debra A. McKeeman  Signature Dates:

Form version date: 4/17/2014
July 24, 2015

To: The IRB, Children's Hospitals and Clinics of Minnesota

RE: Principal Investigator (PI) change:

This is to inform you that Kris Ann P Schultz, MD will become the PI, and Yoav Messinger, MD will be Co-Investigator of the following studies:

1. IRB# 0909-082 International Pleuropulmonary Blastoma (PPB) Treatment and Biology Registry

2. Kris Ann P Schultz, MD will therefore be the PI in charge of all funds in:
   a. Grant 47011 = PPB/Schott & matching funds from the Foundation
   b. Grant 41547 = Pine Tree Apple Tennis Classic
   c. Grant 41837 = PPB Program

Sincerely,

Yoav Messinger, MD
Principal Investigator

cc. Camerone Bey
Rebecca Wright
Pauline Milby
Joy Behrens
Sonya Frisch
Natalie Ruiz
Gretchen Williams
Anne Harris
Ann Blake
Memo

Date: July 6, 2015
To: Debra McKeehen, MS
    IRB Administrator
From: Yoav Messinger, MD
Subject: IRB# 0909-082

Dear Ms. McKeehen,

We write to you in response to your approval with stipulations dated June 10, 2015 re: Principal Investigator (PI) Change for IRB # 0902-082 International Pleuropulmonary Blastoma Treatment and Biology Registry.

1. IRB Stipulation: Please revise consents, assents, and HIPAA authorizations to reflect the change in PI and submit to IRB Administrator. These documents have been revised to reflect the change in PI and are attached below.

Thank you for your attention to this matter.

Sincerely,

Yoav Messinger, MD

Reviewed by Institutional Review Board on 7/10/15
Approved with stipulations. All stipulations now met.
Please note IRB approval date on consent and assent forms, as applicable.

APPROVED by IRB On 7/22/15

Debra A. McKeehen
Debra McKeehen, MS, IRB Administrator