

April 9, 2010

Michael Montello, Pharm.D.
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National Cancer Institute
Executive Plaza North Room 730
Bethesda, MD 20892

RE: Q9403/4941L
REVISION: National Wilms Tumor Study Late Effects of Treatment in
Wilms Tumor Survivors and Offspring

We have revised the above referenced protocol as a result of reviewing the committee and consultants section and study monitoring.

Specific changes are detailed below:

1. Title Page
Updated the NCI protocol number and the revision date on the title page. All pages have been updated with the NCI protocol number.
2. Pages 2-3
NWTS Late Effects Study Committee and Consultants
 - No longer listed is Co-Investigator Debra Friedman, MD. Contact information was updated for Daniel Green, MD, Guilio D'Angio, MD, Vicki Huff, PhD and Michael Ritchey, MD.
3. Page 14
Section 5.0 STUDY MONITORING
 - This section is now replaced with instructions regarding how the DSC will notify institutions and participants before a form is due. Participants will have the option of completing the annual form and returning it in our business reply envelope or of completing the form on the website of SurveyMonkey.com.
4. Appendix A: MODEL CONSENT FORM UNDER 18 YEARS OF AGE
 - The first sentence of the first paragraph has deleted a duplication of "by."
 - The second sentence of the third paragraph of the Family Information packet replaces "2001" with "2006" and "2006" with "2011."
5. Appendix A: MODEL CONSENT FORM OVER 18 YEARS OF AGE
 - The second sentence of the third paragraph of the Information packet replaces "2001" with "2006" and "2006" with "2011."
 - The second sentence of the fourth paragraph of the Information packet put in a space between "years" and "we."
 - The second sentence of the fourth paragraph from the bottom has removed "child's" since this is the consent for over 18 years of age.

I am enclosing both a redlined and a clean version of the Protocol (Q9403/COG 4941L). Please feel free to contact me at 206-543-2035, or DSC Project Manager Patricia Norkool at 206-667-4843, should you have any questions.

Sincerely,

Norman Breslow

Norman Breslow, Ph.D.
Principal Investigator
NWTs Late Effects Study

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Closed:

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NATIONAL WILMS TUMOR LATE EFFECTS STUDY

	<u>Page</u>
Study Coordinators	2-3
1.0 STUDY OBJECTIVES	4
2.0 BACKGROUND	4-9
3.0 PATIENT ELIGIBILITY	9-10
4.0 MATERIAL AND DATA TO BE ACCESSIONED	10-14
5.0 STUDY MONITORING	14-15
6.0 STATISTICAL CONSIDERATIONS	15-17
REFERENCES	18-24

APPENDICES

Appendix A: Model Consent Forms

Appendix B: Information Sheet for Institutions, Informed Consent, Annual mailings

Appendix C: Forms used to ascertain Pregnancies and Births

Appendix D: Forms used to ascertain Familial Wilms Tumor

Appendix E: Forms used to ascertain Targeted Late Conditions

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Data & Statistical Center

1.0 STUDY OBJECTIVES

- 1.1** To determine the incidence of life-threatening medical conditions in survivors of Wilms tumor, specifically a) congestive heart failure; b) second malignant neoplasms (SMNs); c) renal failure; and d) pulmonary fibrosis and interstitial lung disease. To relate the risks of these events to the type and amount of radiation and chemotherapy received;
- 1.2** To determine mortality rates in former Wilms tumor patients and to compare these with age, calendar period, and sex-specific national population rates;
- 1.3** To determine the risks of serious pregnancy complications and other adverse reproductive events in survivors of Wilms tumor, and to correlate their occurrence with the type and amount of radiation and chemotherapy received in childhood. To determine the rates of natality in former Wilms tumor patients and to compare these with national statistics and determine congenital anomalies in offspring;
- 1.4** To determine the frequency of Wilms tumor and other cancers in the children and other family members of Wilms tumor patients. Specifically, a) to estimate the recurrence risk in siblings and offspring; and b) to identify familial cancer syndromes that may involve Wilms tumor patients;
- 1.5** To serve as a case-finding resource, identifying the most informative subgroups of Wilms tumor patients for use by a) molecular biologists studying mutations in identified or prospective Wilms tumor genes including genes for familial Wilms tumor; and b) epidemiologists studying parental occupational exposures and other environmental risk factors.

2.0 BACKGROUND

2.1 Genetic Epidemiology of Wilms Tumor

2.11 A Model for Childhood Cancer

Wilms tumor is an important model for the study of fundamental mechanisms of carcinogenesis. Statistical study of the incidence and age at diagnosis of patients with retinoblastoma led Knudson to develop his famous two-hit model of carcinogenesis, which was subsequently extended to Wilms tumor. [1,2] The genetics of Wilms tumor are more complex than originally believed, however, with several genes now known to be involved in Wilms tumor genesis versus the single gene for retinoblastoma.[3] Epidemiological evidence suggests that some bilateral and multifocal Wilms tumors may arise from somatic mosaicism rather than a germ line mutation, contradicting a central tenet of the two-hit model. [4] Two distinct pathogenetic entities are identifiable on the basis of precursor lesions: perilobar nephrogenic rests (PLNR), which occur in association with growth anomalies; and intralobar nephrogenic rests (ILNR) which occur in association with *WT1* mutations.[5] This provides phenotypic evidence for genetic heterogeneity.

2.12 Wilms Tumor Genes

The observation that the rare WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities and mental retardation) was invariably associated with interstitial deletions of chromosome 11p13, and that tumor tissue at this same locus often displayed loss of heterozygosity (LOH), led ultimately to the cloning of the first Wilms tumor gene *WT1*. [6- 12] Ninety percent of patients with the even rarer Denys-Drash syndrome (DDS: male pseudohermaphroditism, protein-losing nephropathy and Wilms tumor; or males with only 2 of these 3 features; or females with the classically described nephropathy) harbor germ line mutations in *WT1*. Most are missense mutations resulting in single amino acid substitutions. [13-16] Microscopic examination of the kidney in patients with the WAGR and DDS syndromes often reveals ILNR. [17] The frequencies of germ line *WT1* mutations in patients with bilateral Wilms tumor and of detectable *WT1* mutations in Wilms tumor specimens are both low. Linkage at the *WT1* locus has been excluded in most familial cases [18-22] The gene for Beckwith-Wiedemann syndrome (BWS: organ hypertrophy, hyperglossia, perinatal hypoglycemia, abdominal wall defects and propensity for embryonal tumors) maps to chromosome 11p15.5. Here several genes (*IGF2*, *p57KIP2*, *H19*, *KVLQT1*) that regulate somatic growth are subject to dysregulated imprinting. This is the location for the putative second Wilms tumor gene, *WT2*, which has yet to be cloned. [23-29]

2.13 Familial Aggregation and Patterns of Inheritance

The pattern of transmission for hereditary Wilms tumor is likely autosomal dominant with incomplete and variable penetrance and expressivity.[30-33] While some familial cases involve mutations in *WT1*, more are associated with the familial Wilms tumor genes *FWT1* at 17q and *FWT2* at 19q, for which fine scale mapping is currently underway. Further understanding of familial risk is essential for counseling the rapidly increasing pool of survivors and to provide valuable information to molecular biologists attempting to isolate the gene(s) responsible.

2.2 Long Term Consequences of Childhood Cancer Treatment

Five year survival percentages for patients enrolled in National Wilms Tumor (NWTs) protocols were 79.7% for 1969-74 enrollees, 81.6% for 1975-1979, 86.3% for 1980-84, 88.6% for 1985-1989 and 90.4% for 1990-1995, and are among the highest for childhood cancer. Despite similar treatment, only some survivors develop late complications of therapy. Studies to date have identified several of the most serious complications. Specific disease, treatment and host related risk factors, however, require further investigation. The systematically treated and followed NWTs cohort is ideal for study of these questions.

2.21 Gonadal Function and Fertility

The effect of radiation on reproductive function is dose and age dependent. [34, 35] In an NCI study, Byrne and colleagues found relative fertility (compared with sibling controls) was 0.75 for female cancer survivors receiving sub-diaphragmatic radiation. For the subgroup of 29 Wilms tumor survivors, relative fertility was 1.47 (95% C.I. 0.81-2.65). Females treated in the pre-pubertal years did not experience premature menopause. [36, 37] Chiarelli and colleagues studied a similar Canadian cohort, of whom 46 had Wilms tumor. Women treated with abdominal-pelvic radiation without the use of alkylating agents had a relative risk of early menopause of 1.62 and a relative fertility of 0.77, neither of which was statistically significant.[38] Neither study included sufficient numbers of Wilms tumor patients for stable statistical results. Small studies of Wilms

tumor survivors have indicated that ovaries or uterus may be decreased in size in those who received whole abdomen radiation therapy (RT). [39, 40] This may affect both fertility and pregnancy outcomes and requires additional study. Testicular radiation can cause azoospermia, due to scatter from abdominal-pelvic radiation. [41, 42] Studies with substantially larger numbers of patient are needed, however, to definitively investigate these issues.

2.22 Pregnancy Outcomes

Adverse pregnancy outcomes have been reported in Wilms tumor survivors treated with abdominal radiation prior to 1980.[43-46] Rates of perinatal mortality and low birth weight were eight and four times higher, respectively, than among US white women.[46] Female survivors were four times more likely than sibling controls to have adverse outcomes such as low birth weight, preterm delivery, birth defects and neonatal death. This was not seen in the wives of male survivors. [43] Further follow-up of the NWTs cohort will vastly increase the numbers of patient offspring available for such studies.

2.23 Second Malignant Neoplasms

Survivors of childhood cancer are at increased risk of developing a second malignant neoplasm (SMN). The cumulative risk at 20 years varies between 3-10% over several studies and is 5-20 times greater than that expected in the general population.[47-51] The incidence of SMNs following Wilms tumor in NWTs patients was initially reported in 1988 for those patients enrolled between 1969 and 1982. Fifteen SMNs were identified among 2,438 patients. The observed (O) to expected (E) or standardized incidence ratio (SIR) was 8.5 (4.7-14.0). [52] The 4 patients who developed hepatocellular carcinoma all had right-sided tumors for which they received flank radiation. None had cirrhosis and neither of 2 tested had positive serology for Hepatitis B. Three of the 4 had a congenital anomaly or other heritable disease, suggesting the potential for an unstable genome. [53] These results were updated in 1996 based on follow-up through 1993 of 5,278 patients enrolled through 1991. A similar SIR of 8.4, with 43 SMNs, was observed.[54]

The Childhood Cancer Survivor Study (CCSS) reported 14 SMNs among 1,174 survivors of Wilms tumor for an SIR of 6.0 (3.4-9.9) and a 20-year cumulative risk of SMN of 1.6%.[47] Three breast cancers were found and the relative risk in multivariate analysis was 12.4 (1.9-78.7). Because of the long latency period for breast cancer and other solid tumors, survivors of Wilms tumor from the CCSS and NWTs cohorts are just now beginning to reach the ages at which substantial numbers of excess cancers may be expected. Large numbers of patients were treated with doxorubicin, a radiation sensitizer and topoisomerase II inhibitors, only after 1980. Continued follow-up is essential to determine the long term risk posed by doxorubicin and to confirm or refute the suggestion from the second NWTs study that exposure to chemotherapy alone, without radiation, may itself increase the risk of second malignancies.[54]

2.24 Contralateral Wilms Tumor

Children with bilateral Wilms tumor, either at initial diagnosis or subsequently, have a lower overall survival and a higher incidence of renal failure. [55-57] Bilateral disease, whether synchronous or metachronous, is strongly associated with the precursors ILNR and PLNR.[5] Children who develop another Wilms tumor in the contralateral kidney are generally believed to have a genetic predisposition, in accordance with Knudson's theory. Prediction of who these patients may be at the time of initial diagnosis is important to facilitate renal

sparing surgery and follow-up by ultrasound. The NWTs study by Coppes and colleagues identified the joint presence of PLNR and ILNR, or the presence of PLNR in children diagnosed during the first year of life, as important risk factors. [58] These features did not predict all the future events, however, and further study is warranted to determine others.

2.25 Cardiac Toxicity

Wilms tumor patients may have two risk factors for cardiac toxicity, exposure to doxorubicin and radiation (thoracic and left flank). Cardiac toxicity may be symptomatic or purely subclinical. [59-64] Cardiomyopathy risk from anthracyclines may be increased in females, those with higher cumulative doses, and younger age at diagnosis, and with longer follow-up time. [62-65] It is plausible to postulate that long-term survivors of Wilms tumor may be at uniquely increased risk of cardiac toxicity due to combination of radiation therapy and radiation sensitizing chemotherapeutic agents. The first NWTs study of cardiac toxicity demonstrated that risk of congestive heart failure persisted for 8-12 years or more from the time of anthracycline treatment. Since anthracycline was used more extensively in NWTs 3-4 than it had been earlier, continued follow-up is again essential in order to determine whether the risk may persist even longer than now believed.

2.26 Renal Failure

Children with Wilms tumor are at risk of renal dysfunction and/or failure from a variety of potential mechanisms including radiation therapy, use of potentially nephrotoxic chemotherapy agents, and a theoretical risk due to hyperfiltration of the remaining nephrons following removal of a critical mass of renal tissue. [55, 66-68] There is a genetic component also. Patients with the Denys-Drash syndrome have a characteristic severe nephropathy believed to be due to a dominant negative effect of the *WT1* mutation. [14] Hypertension may be a surrogate marker for some degree of renal dysfunction. Finkelstein and colleagues documented an increased incidence of diastolic hypertension among survivors of Wilms tumor, especially at younger ages. [69]

In 1996, Ritchey and colleagues reported the spectrum of renal failure in 55 patients among 5,823 patients treated on NWTs 1-4. [57] The cumulative risk of renal failure at 16 years was 0.6% for all unilateral patients, and 13% for NWTs-3 bilateral patients. The most common etiologies of renal failure were bilateral nephrectomy for persistent or recurrent tumor, progressive tumor in the remaining kidney without nephrectomy, Denys-Drash syndrome and radiation nephritis. [57] A more recent NWTs report revealed that patients with the WAGR syndrome were at very high risk of renal failure after puberty. [70] The long term cumulative risks of renal failure for patients with a missense *WT1* mutation (DDS) or a chromosomal deletion of *WT1* (WAGR) were thus both in excess of 50%. More detailed study of the renal pathology in both syndromes is needed to determine whether it may have a common genetic origin. Further follow-up is also needed to determine whether other patient subgroups with possible *WT1* mutations giving rise to less severe phenotypes, identified by the presence of GU anomalies or ILNR, also have a high if not extreme incidence of renal failure.

2.27 Pulmonary function

Delayed lung toxicity may occur after treatment with radiation or chemotherapy. [71, 72] While none of the chemotherapeutic agents used in Wilms tumor is known to induce pulmonary toxicity, doxorubicin and dactinomycin may augment the radiation effect. Both early interstitial lung disease and later occurring pulmonary fibrotic disease are seen after radiation therapy for other malignancies. [71, 73] It is therefore

important to assess the incidence of this long-term effect in survivors of Wilms tumor, especially in those also at risk for cardiac dysfunction.

2.28 Mortality Among Survivors of Wilms Tumor

From 1975-1995, there has been a dramatic decrease in childhood cancer mortality. [74] However, long-term sequelae may result in later cancer and non-cancer related mortality, including second malignancies, cardiac and pulmonary disease and infection. [75-79] Treatment with doxorubicin, alkylating agents or radiation therapy increases risk. [75, 79] The standardized mortality ratio observed for the CCSS cohort was 9.6 (9.2-10.1) overall and 14.1, based on 68 deaths, for the 1,174 5-year survivors of Wilms tumor. Cumulative mortality (beyond 5 years) was 1.8, 3.1 and 5.0% at 10, 15, and 20 years respectively. [75] The large unselected NWTS cohort, with over 5,000 5-year survivors (Table 1), should provide much more accurate results. It also has the advantage of complete follow-up of patients from diagnosis. By identifying the treatment and host factors associated with the excess mortality, interventions may be developed and targeted for those at highest risk. Now that 90% of children with Wilms tumor are being cured, it is most important to focus attention on the duration and quality of life in the survivors.

TABLE 1: NWTS patients eligible for Late Effects Study*

Year of Registration	Randomized	Followed	Total
1969-1974	365	204	569
1975-1979	673	260	933
1980-1984	1176	355	1531
1985-1989	851	786	1637
1990-1995	955	859	1814
Total	4020	2464	6484

* Patients from US and Canadian institutions

TABLE 2: Comparison of NWTS AND SEER populations, 1973-1995 by gender, age at diagnosis and race

	NWTS *		SEER **	
	#	%	#	%
Male	2819	47.7	497	48.5
Female	3092	52.3	527	51.5
0-4 years	4506	76.2	743	72.6
5-9 years	1236	20.9	226	22.1
10-14 years	169	2.8	55	5.4
Caucasian/Hispanic	4747	80.3	817	79.8
African American	1036	17.5	157	15.3
Other/Unknown	128	2.2	50	4.9
Total	5911	100	1024	100

*US institutions only; **Population based

2.3 Description of the NWTS Cohort

2.31 NWTS Study Population

Five therapeutic studies have been completed: NWTS-1 (1969-1974), NWTS-2 (1975-1979), NWTS-3 (1980-1985), NWTS-4 (1986-1995), and NWTS-5 (1995-2002). Approximately 70-80% of the total national US incidence of Wilms tumor have been registered on these studies since 1980. Table 1 shows patients treated on NWTS 1-4 who are eligible for the Late Effects Study.

Table 2 contrasts the age, gender, and race distributions of 1973-1995 Wilms tumor patients registered with the NWTS from US institutions with those from the same time period reported by the SEER program. [80] No

differences are evident in gender or racial composition. Older patients are slightly under-represented in the NWTS compared to SEER.

TABLE 3: Percentage of NWTS patients from US and Canadian institutions estimated to be alive at 5 and 10 years since diagnosis, and number actually followed, by calendar period of registration

Year Registered	Patients	Percent alive *		# Estimated alive		# Followed alive	
		5 yrs	10 yrs	5 yrs	10 yrs	5 yrs	10 yrs
1969 – 1974	569	79.7	77.9	453	443	444	421
1975 – 1979	933	81.6	80.2	761	748	719	665
1980 – 1984	1,531	86.3	85.3	1,321	1,306	1,248	1,137
1985 – 1989	1,637	88.6	87.1	1,450	1,426	1,351	1,040
1990 – 1995	1,814	90.4	87.4	1,640	1,585	1,281	64 **
Total	6,484	86.8	85.2	5,625	5,508	5,043	3,327**

*Actuarial estimates; **Many of these patients have not had opportunity for 10 year follow-up.

Cure rates for Wilms tumor, among the highest in pediatric oncology, have steadily increased over successive NWTS studies. Considering all patients on the Late Effects Study, it is estimated that 5,625 have survived >5 years from diagnosis and 5,508 will have survived >10 years (Table 3). The numbers actually followed and known to be alive at those time points are of course smaller, due to the inevitable losses to follow-up and delays in information flow. At last follow-up, 5,498 patients were known to be alive (Table 3).

2.32 Histopathology

All patients on successive NWTS protocols are required to have slides submitted to the study pathology center for centralized review and since, 1980, for the presence, number and type of precursor lesions. This has been successful in 90% of all eligible NWTS-1, 91% of NWTS-2, 94% of NWTS-3, 97% of NWTS-4 and 99% of NWTS-5 patients. Tissue is archived for use in clinical or special research studies. In NWTS-5, a biology study was added to the therapeutic protocol. The NWTS Tissue Bank has biologic specimens for 72% of eligible patients.

2.33 Treatment

Detailed therapy records are collected prospectively for all patients and entered into a computerized database at the NWTS for initial and, when applicable, retrieval therapy. Both randomized and historical comparison groups are available for evaluation of the effect of radiation and chemotherapy on the endpoints of interest. Radiation was part of standard treatment for all patients on NWTS-1, but is employed at much reduced doses for only 40% of patients on NWTS-4,5.

3.0 PATIENT ELIGIBILITY

- 3.1 NWTS-1 through NWTS-4: Registration procedures for entry onto NWTS-1 through NWTS-4 included obtaining written consent from the patient's parents for participation in the study, including collection of follow-up data for an indefinite period. These patients were automatically eligible for the Late Effects Study when they reached their second anniversary following diagnosis. There was no separate consent or registration for these patients.

- 3.2 NWTS-5: Institutions should complete and submit a Participant Entry Questionnaire (PEQ). See below. If the institution's original consent allowed for long term follow-up, the institution need merely notify the Data and Statistical Center (DSC) that their patients are consented. Starting with the 9/01 revision of the protocol, NWTS-5 patients can be re-consented and thus registered on the Late Effects Study. Do not report the registration using the COG RDE. At the time the institution informs the DSC of a newly consented patient it should also report the date of contact, the method of contact, and the status of the patient's health. The DSC can then code a new date of follow-up which will be included in the report to COG. The DSC will report to COG quarterly.

NWTS-5 patients are eligible if they:

- 3.21 Were registered as a Studied or Followed patient on NWTS-5;
- 3.22 Were <16 years of age at the time of diagnosis of a stage I-V favorable histology Wilms tumor, stage I-V focal or diffuse, anaplastic Wilms tumor, stage I-V clear cell sarcoma of the kidney (CCSK) or stage I - V rhabdoid tumor of the kidney (RTK), including those tumors with any of the above histologies which occurred in fused (horseshoe or discoid) kidneys, or a solitary kidney, or at an extra-renal site; and
- 3.23 Survived for two years after diagnosis.

4.0 MATERIAL AND DATA TO BE ACCESSIONED

The NWTS Data and Statistical Center (DSC) will provide institutions and families in direct contact with the appropriate forms approximately three months before they are due, **with the exception of flowsheets.**

NWTS Annual Status Reports (ASRs) should be submitted starting in year 2 to document patient contact. At any time a patient relapses, flowsheets and complete clinical documentation must be submitted. Please see section 4.84.

- 4.1 **Participant Entry Questionnaire (PEQ)** – All institutions should complete and submit a PEQ in order to inform the NWTS if the Late Effects Study protocol has received IRB approval, and if approved, whether or not they must re-consent NWTS-5 patients.
- 4.2 **Informed Consent (IC)** - The Data and Statistical Center (DSC) will request that the institution document Informed Consent for NWTS-5 patients eligible for accrual to the Late Effect Study after the second anniversary following diagnosis. This request is accompanied by a letter of instruction to the institution, an information sheet for institutions, two model consent forms, and a Family Information Packet that is to be forwarded to the family. Immediate documentation of Informed Consent will help avoid losing patients from long term follow-up and will constitute accrual to the Late Effects Study. A copy of this packet may be found in the appendix.
- 4.3 **Family Information Packet (FIP)** - The DSC will send this to the institution to be forwarded to the family at the time the patient is eligible for accrual. This packet describes the study and schedule of forms and should be forwarded to the family immediately. This packet is shown in the Appendix.

- 4.4 Medical History Forms** - Institutions are requested to present the Medical History Forms to families whenever possible and to not complete them with data found in files.
- 4.41 Adult Patient Medical History Form (APMHF)** - This form is requested every five years, on the fifth, tenth, fifteenth, twentieth, etc. anniversaries of diagnosis, from patients who are 18 years of age or older.
- 4.42 Family and Medical History Form (FMHF)** - This form is given to/sent to the parents of patients who are less than 18 years of age at the fifth, tenth, and fifteenth anniversaries of diagnosis, as appropriate.
- 4.5 NWTS Late Effects Study Physical Examination (PE)** - This form is to be completed by the current physician of record for the patient at every fifth anniversary after diagnosis. It is mailed from the DSC to the current institution of record for patients remaining in follow-up by the institution, and directly to the family/patient for patients who are under direct follow-up by the DSC.
- 4.6 NWTS Late Effects Study Annual Status Report (ASR)** - This form is requested starting on the sixth year following diagnosis and may be completed by the current physician of record for the patient at each yearly anniversary (excluding the multiples of the fifth anniversary) after diagnosis. It is mailed from the DSC to the current institution of record for patients remaining in follow-up by the institution, and directly to the family/patient for patients who are under direct follow-up by the DSC.
- 4.7 NWTS Adult Consent Form (ACF)** - When each patient turns 18 years of age, the DSC solicits his/her continuing informed consent for participation in the Late Effects Study. The ACF is sent to the institution, local physician, patient or patient's family at that time, together with a cover letter and information sheet.

TABLE 4: Submission of Long-Term Follow-Up Forms

18th Birthday Adult Consent Form

Years Since Diagnosis	Form(s) to be Submitted	Years Since Diagnosis	Form(s) to be Submitted
2	Informed Consent, FIP, Flowsheets	12	Annual Status Report
3	Flowsheets	13	Annual Status Report
4	Flowsheets	14	Annual Status Report
5	Physical Exam, FMHF/APMHF	15	Physical Exam, FMHF/APMHF
6	Annual Status Report	16	Annual Status Report
7	Annual Status Report	17	Annual Status Report
8	Annual Status Report	18	Annual Status Report
9	Annual Status Report	19	Annual Status Report
10	Physical Exam, FMHF/APMHF	20	Physical Exam, FMHF/APMHF
11	Annual Status Report		

Continue with five year cycle of form submission

4.8 Requests for Medical Records

The key events monitored by the DSC include pregnancies and births, cancer and congenital malformations in offspring, Wilms tumor in any family member, second malignant neoplasms, heart, lung, and renal disease and death. As soon as one of these events is ascertained, further details are requested from the appropriate source. When this entails going beyond the standard follow-up procedure to which the family already has consented as part of the therapeutic trial, appropriate authorization for release of medical information is solicited.

4.81 Pregnancies and Births

A Pregnancy Questionnaire and authorization for Release of Medical Information are mailed to the NWTs patient as soon as the DSC learns about a pregnancy or birth. This covers items about the hospital where the birth took place, pregnancy complications and outcome, and birth defects, childhood illnesses and survival in the offspring. It requests an authorization for release of medical records on mother and child for access to the medical history of the pregnancy, delivery and early childhood. Copies of the birth certificate may be requested. Once a child is known to have been born to the NWTs patient or partner, permission is sought to request annual updates on the health status of that child. Should sentinel events be detected, permission is sought for the release of additional medical records. The forms used in this process are shown in the Appendix.

4.82 Familial Wilms Tumor

Cases of familial Wilms tumor are ascertained from the registration form and family questionnaire filled out at the time of the initial diagnosis as well as from the medical history forms and annual updates utilized as part of the Late Effects Study. Confirmation of the pathology diagnosis and some information about the histology and laterality of the tumor is sought for all familial cases not already registered on the NWTs.

To protect the privacy of extended family members a packet is sent to families in direct contact containing a letter explaining our request, a second letter which we request be forwarded to the extended family, a postcard for their reply, and an authorization for us to contact the hospital/physician where the extended family member was diagnosed/treated for Wilms tumor.

When a patient is followed by an institution a page for the CRA to fax to the DSC is included to indicate a) if the institution will forward the packet to the family, and b) if the institution cannot contact the family that they will return a signed familial release so that the DSC may contact the family directly.

Forms used in this process are shown in the Appendix. Pedigrees of the immediate family (parents, siblings and offspring) are constructed from data supplied on the medical history and annual update forms. Telephone follow-up may be undertaken in cases where the entries are incomplete or ambiguous.

4.83 Second Malignant Neoplasms and Organ System Failures

A copy of the pathology diagnosis or other clinical reports are requested for all identified second malignant neoplasms; only those SMNs with pathology confirmation are utilized in statistical analyses. Clinical records, reports of imaging studies and autopsy reports may also be requested. A similar procedure is followed to document identified cases of organ system failures. If such conditions are initially reported by the original institution, further details are requested directly from that institution just as they are for the clinical trial. If reported by the patient, the family or a local physician, however, permission for release of medical records is sought before approaching the physician/institution where the diagnosis was made. The forms sent to the family or (adult) patient that authorize the collection of such data are shown in the Appendix.

4.84 Relapse

In the event of a relapse in a patient in institutional contact, follow-up should be submitted monthly until a complete response is attained to the Data and Statistical Center. Whenever the patient develops recurrence or metastases, send the DSC the flow sheet giving the details of the relapse. If surgery is performed, a copy of the operative note and a copy of the pathology narrative should also be forwarded to the DSC. Events to be documented: progression or regression of disease, method of detection (radiology reports, surgeries, etc.), dates of each and treatment summary.

4.85 Death

In the event of the death of a patient in institutional contact the following information should be submitted: flowsheets, a Post Mortem Checklist, and autopsy report.

4.9 Coding of Medical Conditions

4.91 In Patients

Specified medical conditions identified in NWTS survivors are coded in a record that contains (i) date of diagnosis; (ii) 5-digit International Classification of Disease (ICD) code; (iii) 6-digit morphology/malignancy code for neoplasms (ICD); (iv) an alphanumeric description; (v) the initial and best source of information (pathology, clinical report, PE form, etc.). A dictionary of previously detected conditions with corresponding ICD codes is used by DSC staff as an adjunct to the ICD manuals.

4.92 In Offspring of Patients

4.921 Birth through Age Six- Medical conditions reported in patients' offspring are coded using the Metropolitan Atlanta Congenital Defect Program Manual (MACDPM). Data items coded are the same as for conditions coded in patients. Additional coding includes the MACDPM inclusion or exclusion designation.

- 4.922 After Six Years Old** - All medical conditions identified in NWTS survivors are coded in a record that contains (i) date of diagnosis; (ii) 5-digit International Classification of Disease (ICD) code; (iii) 6-digit morphology/malignancy code for neoplasms (ICD); (iv) an alphanumeric description; (v) the initial and best source of information (pathology, clinical report, PE form, etc.).

5.0 STUDY MONITORING

The DSC will notify institutions and participants approximately three months before a form is due. Participants have the option of completing the annual form and returning it to the DSC in the business reply envelope provided or of going to the website of SurveyMonkey.com to complete the form electronically in the area to which the DSC has access. The DSC will notify by email those participants who have notified us they prefer to complete electronic forms and have provided the DSC with their email addresses. All other participants will receive their annual form by mail.

- 5.1** All surviving NWTS 1-5 patients in the Randomized, Studied and Followed categories who have survived at least two years are eligible to be participants in the Late Effects Study.

5.12 Patients from National Wilms Tumor Studies 1-4

The institutions have received an NWTS Late Effects Study Information Sheet and a packet to be sent to the family that discusses the study and the schedule of forms. If the patient is no longer returning to the institution, a Release Authorization is solicited requesting that the DSC be authorized to trace and contact the family for continued follow-up. **If the institution is unable to return a signed authorization for any reason they are asked to please call the DSC immediately at (206) 667-4842.**

5.13 Patients from National Wilms Tumor Study 5

- 5.131 If the NWTS-5 informed consent provided for long-term follow-up, the institution need only inform the DSC that its patients are already consented by submitting the PEQ. For patients not yet consented to long-term follow-up, the DSC will send informed consent packets and Family Information Packets for all eligible patients to the institution. These packets will discuss the study and the schedule of forms and the Family Information Packet should be forwarded to the family immediately.

- 5.132 At the time the institution informs the DSC of a newly consented patient it should also report the date of contact, the method of contact, and the status of the patient's health. The DSC can then code a new date of follow-up which will be included in the quarterly report to COG.

- 5.133 **If a patient is no longer returning to the institution, a Release Authorization is solicited requesting that the DSC be authorized to trace and contact the family for continued follow-up. If an institution is unable to return a signed authorization for any reason they are asked to please call the DSC immediately.**

- 5.2** Between the second anniversary from registration and the fifth anniversary, the treating institution will continue to submit flowsheets for all contacts with the patient.

- 5.3** On the fifth anniversary, the NWTS DSC will send a packet containing the NWTS Late Effects Study Physical Examination Form and the NWTS Late Effects Study Family Medical History Form to the physician of record, or to the family if the DSC has been authorized to contact them directly. This packet contains a cover letter explaining the study forms and data collection schedule, and requesting the patient's continued participation. The letter notes that patients may discontinue their participation at any time by contacting the DSC. No further attempts at contact are made for patients who discontinue participation.
- 5.4** The NWTS Late Effects Study Annual Status Report is sent to all patients under direct contact by the DSC, or to the physician of record, for patients remaining under the care of the original treating or another physician. Please refer to Table 4 for the schedule.

6.0 STATISTICAL CONSIDERATIONS

6.1 Sample Size and Study Design

6.11 Estimation and Comparison of Event Rates

The methods of statistical analysis to be used in this study are those appropriate to the analysis of follow-up (cohort) studies more generally. They include estimation of incidence rates of major study endpoints, comparison of such rates with national standards (where available) and internal comparisons between different patient subgroups defined on the basis of their treatment, or on the basis of congenital anomalies and precursor lesions that may indicate different types of genetic predisposition. Relative risk regression analyses are used to model the incidence rates as a function of multiple quantitative or qualitative characteristics. Much of the relevant methodology had been developed or reviewed by Dr. Breslow and his collaborator Dr. N.E. Day in a 1987 IARC monograph [123] which together with a volume on case-control studies [124] is now a standard source for statistical methods in epidemiology.

6.12 Nested Case-Control and Case-Cohort Studies

For specific adverse events (such as pulmonary or cardiac toxicity) we plan additional analyses using a nested case-control or case-cohort approach. This will permit the efficient abstraction, or if needed the collection and abstraction, of more extensive data than are already in the NWTS computerized data base. Cases are those who have had the endpoint of study (e.g. pulmonary fibrosis). Controls, without the endpoint of interest, are chosen randomly at a rate of 4 or more controls per case. Such an approach allows for approximately 80% efficiency relative to the analysis of all available controls and thus is quite cost-effective when an endpoint is rare and substantial additional data need to be collected or abstracted.

Dr. Breslow's current methodologic research is focused on the design and analysis of stratified case-control and case-cohort studies that enable all the information already available in computer files, on both outcome and exposure, to be utilized in the most efficient way possible.[125] The substantial gains that may be realized in comparison with more

conventional designs and less efficient analyses were illustrated recently by application to NWTs prognostic factor studies.[126] Software is available for stratified case-cohort as well as stratified and nested case-control studies.[127] The availability of this expertise and software will be a major boon to the studies proposed in this application.

6.13 Studies of Familial Aggregation

For the family history study performed to examine for aggregations of cancer among NWTs family members, standardized incidence ratios (SIR) of observed to expected malignancies were calculated using age- and sex-specific incidence rates. [80] Generalized estimating equation (GEE) methodology is used to account for intrafamilial correlations. [128]

6.14 Longitudinal (Repeated Measures) Data Analysis

Analysis of longitudinal data involving repeated measures on each patient will use methods for linear and nonlinear regression with random effects that explicitly model the correlation structure, as was done for the recently completed analysis of stature [128] as well as more robust methods based on generalized estimating equations. [129]

6.15 Projected Number of Events and Power Calculations

Once follow-up is complete, we expect to have accumulated over 75,000 person-years of observation through 1999. Judging from the studies already successfully completed, this will be adequate to answer many questions of scientific interest. For example, using the additional follow-up projected for the 1995-99 period over that already observed, the number of SMNs expected SEER rates for the period 1969-99 is 14.3. Assuming the historical O/E ratio of 8 is maintained, we anticipate having 114 SMNs for analysis once ascertainment is complete and medical records have been reviewed. This will permit relative risks of 2.0 or less to be detected for most of the internal comparisons that one might contemplate, provided that the comparison groups are not extremely unbalanced (Table 6). An important issue will be to determine whether patients treated with chemotherapy alone (no radiation) are at increased risk of cancer (§2.23) Approximately 47% of the person years through 1999 were contributed by patients who did not receive radiation, and their expected number of SMNs is at least 5.0. This is sufficient to detect a relative risk of 2.5 using a 5% test with 80% power (Table 7.3 of [123]). Even greater sensitivity will be achieved by incorporating events that occur during the years 2000 and 2001.

TABLE 5: Person-years (PY) of follow-up; observed and expected numbers of new cancers (1969-99)

Subgroup	No. patients	PY	Observed*	Expected**	SIR=O/E***	95% CI SIR
Males	3,091	33,743	33 (+2)	5.93	5.6	(3.8, 7.8)
Females	3,393	37,244	37 (+2)	6.34	5.8	(4.1, 8.0)
By time since diagnosis (years)						
0 –	6,484	28,335	19	4.01	4.7	(2.9, 7.4)
5 –	5,042	20,669	15 (+4)	2.48	6.1	(3.4, 10.0)
10 –	3,322	12,662	13	2.27	5.7	(3.1, 9.8)
15 –	1,896	9,321	23 (+1)	3.52	6.5	(4.1, 9.7)

* Numbers in parentheses are third malignant neoplasms; ** Using follow-up only until first SMN; *** first SMN

TABLE 6: Expected number of cases in the control group required to detect a difference with 5% significance and 80% power when the control group is K times the size of the exposed group (from Table 7.4 of [123])

Relative risk	$K=1/10$	$K=1/5$	$K=1/2$	$K=1$	$K=2$	$K=5$	$K=10$
2	11.3	12.3	15.1	20.0	29.6	58.6	107
3	3.9	4.2	5.2	6.7	9.9	19.5	35.0

The expected number of live births to female survivors through 1999, assuming natality according to standard rates, is 982. This number of births is unlikely to be ascertained due to impaired reproductive capacity, a decision on the part of patients to delay childbirth, and some incompleteness of follow-up. Using the ratio of observed to expected of 0.44 for 1990-94, it is projected that pregnancy questionnaire data and medical records will be collected for 432 live births that occurred before 2000 in female survivors, and similarly for 153 children of male survivors. These numbers compare favorably with those used in other studies of reproductive outcomes [43-46]. Furthermore, with anticipated follow-up of these 585 offspring for at least 5 years by the time of analysis, most of them will have lived past the period of greatest risk for Wilms tumor. Using the rates of bilaterality in familial and non-familial cases, the hereditary fraction under the two-stage model is 44% overall and 40% in patients with unilateral disease. [2] Assuming the low penetrance of 20% recently estimated for *FWT1* [33] the recurrence risk may be as high as 4%. The actual risk will be estimated using likelihood methods that account for the multiple affected offspring that may occur in some families and the fact that not all of them will be completely beyond the period of risk.

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PATIENT MODEL CONSENT FORM
National Wilms Tumor Late Effects Study

CONSENT FORM: UNDER 18 YEARS OF AGE

I, _____, willingly agree to allow my child to participate in this investigation, which has been explained to me by _____. This research study is being conducted by the National Wilms Tumor Study (NWTs) and by _____.
(Institution)

The purpose of this research is to learn more about the possible causes of Wilms tumor and the effects of successful treatment for Wilms tumor. I have been asked to be in this voluntary study because my child had a Wilms tumor and has completed therapy for the tumor. I have read and understand the two-page explanation of the purpose of this research study, and of the potential risks and benefits of participation, which is attached to this consent form. To determine the long-term effects of the treatment which has been given to my child, s/he will be evaluated once per year by her/his own physician or, if my child doesn't have a physician, by completing a brief questionnaire. This research study involves the completion of several forms requiring information about my child's family and my child's current state of health. Depending upon my child's health status, I may also be asked to allow copies of my child's past medical records to be sent to the NWTs Data and Statistical Center. This study does not specifically involve obtaining any blood tests. These will be obtained at the discretion of my child's doctor.

POTENTIAL BENEFITS: Although there may be no direct benefit to my child through participation in this study, other children who need treatment for Wilms tumor, the children's parents, and the health care professionals who take care of those children may benefit from increased knowledge about the children with Wilms tumor.

I understand that I will not be charged additional expenses for my child's participation in this study. I also understand that I will not receive money for participation in this study. I understand that I am free to withdraw my consent to allow my child to participate in this study. I may withdraw consent at any time and this decision will not adversely affect my child's care at this institution or cause a loss of benefits to which my child might be otherwise entitled.

All data obtained from this research will remain confidential and will only be used for biomedical research. The confidentiality of this document and all records from this research will be protected to the extent provided by law. Neither my child's name nor any other family member's name will be used in any report.

My signature below indicates that I have read all the above information, received answers concerning areas I do not understand, and am willingly giving my consent for my child to participate in this program. On signing this form, I will receive a copy.

Parent, Guardian

Date

Patient

Date

Witness

Date

Physician

Date

LATE EFFECTS STUDY **CONSENT FORM PAGE 2: UNDER 18 YEARS OF AGE**
FAMILY INFORMATION PACKET

You are being asked to allow your child to continue participation in this study because your child was previously treated for Wilms tumor on the NWTS-5 protocol. This research project includes only people who choose to take part in it. Please consider the following information and take your time in making your decision.

WHY IS THIS STUDY BEING DONE?

The Late Effects Study is being conducted in order to answer scientific questions and to serve as a resource for Wilms tumor patients and their families. Although most people in this study enjoy good health, some may be at risk for certain health conditions. We are collecting information from as many participants as possible in order to determine if they or their offspring are at risk for adverse medical conditions. If there is more than one case of Wilms tumor in a given family, we plan to work with geneticists to try to estimate heritability and recurrence risks. We would like to answer your questions about possible long-term effects of treatment for Wilms tumor. This is why we are collecting information on health issues and pregnancies.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Over 5,000 people have chosen to participate in this study. We expect that more people will enroll as we contact them to continue participation, at least 1,500 between December 2006 and November 2011.

WHAT DOES PARTICIPATION INVOLVE?

Every five years we will send a Medical History Form for you to fill out and a Physical Exam Form for your child's physician to complete and return. In each of the intervening four years we send an annual request. This Annual Status Report asks about significant health events and confirms your most recent address.

Reports of conditions of particular interest are followed up with requests for consent to obtain confirming medical records. Current conditions of interest include pregnancy in participant or partner, heart, kidney or lung conditions, the development of other cancers, and the diagnosis of Wilms tumor in a family member.

We will always enclose return envelopes for your convenience.

WHAT IF MY CHILD IS NOT SEEING A PHYSICIAN?

When we send the Physical Exam Form every five years we understand that a visit to a health care provider may be a prohibitive expense for some. Completion of this form is not a requirement for participation. Although we recommend continued medical care, we would like to continue hearing from you regardless of your child's ability to be seen by a health care provider.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to allow your child to continue participation in this study your family may not personally experience any medical benefits. However, you may benefit by the resources we provide when you contact us for information or advice. Members of our national committee stand ready to answer, as knowledgeably as possible, any questions you may have.

We believe that the information we collect about your child and other participants will benefit other people diagnosed with or touched by Wilms tumor. Already people entered on the NWTS protocols have contributed enormously to our ability to successfully treat a new generation of children with Wilms tumor. By continuing to gather information on your child's current health we hope to learn about any risks associated with treatment for Wilms tumor.

LATE EFFECTS STUDY **CONSENT FORM PAGE 3: UNDER 18 YEARS OF AGE**
FAMILY INFORMATION PACKET CONTINUED

WHAT ARE THE RISKS OF THE STUDY?

We respect that parents have different comfort levels with sharing certain aspects of their children's medical history. This discomfort is the primary risk of participation. However, we ask that you let us know if there is a particular part of our study for which you would rather not provide information. When we ask for annual updates you may decline to provide answers or releases for medical records if you are uncomfortable in sharing this information. Please let us know if you do not want to answer a particular question.

HOW LONG WILL MY CHILD BE IN THE STUDY?

We would like your family to participate in this study until the research is completed. However, you may withdraw at any time. We hope that you decide to continue participating and help us with this important research. However, if you decide to withdraw your consent to allow your child to participate in the study, we encourage you to talk to your child's regular doctor first and to retain the information in this document so that you may contact us in the future. We remain available to you as a resource regardless of your participation status.

WHAT ABOUT CONFIDENTIALITY?

Extensive efforts will be made to keep your family's personal information confidential. We cannot guarantee absolute confidentiality, but only those involved in the science of the study will be granted access to your child's medical records. Your child's personal identity will not be revealed in any publication or report.

In order to ensure compliance with the laws that govern research, the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board (IRB) will periodically audit studies. As part of their audit process, the IRB may review your child's medical records as they pertain to this protocol to ensure that the informed consent process was conducted properly. If you have any questions about this review process, you may call Karen Hansen, Director of the FHCRC Institutional Review Office at (206) 667-4867.

WHAT ARE THE COSTS?

This study makes no payments to participants for taking part in the study. We are also unable to provide any money for medical examinations or treatment.

WHAT ARE MY CHILD'S RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or your child may leave the study at any time. Again, you may contact Karen Hansen at the phone number above regarding your rights as a research participant.

WHOM DO I CALL FOR MORE INFORMATION OR IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study please call Dr. Norman Breslow at (800) 553-4878. Dr. Breslow is the Principal Investigator of the Late Effects Study, and the NWTs Statistician. You may also visit the website of the Data and Statistical Center at <http://www.nwtsg.org>.

PATIENT MODEL CONSENT FORM
National Wilms Tumor Late Effects Study

CONSENT FORM: OVER 18 YEARS OF AGE

I, _____, willingly agree to participate in this investigation, which has been explained to me by _____. This research study is being conducted by the National Wilms Tumor Study (NWTS) and by _____.
(Institution)

The purpose of this research is to learn more about the possible causes of Wilms tumor and the effects of successful treatment for Wilms tumor. I have been asked to be in this voluntary study because I had a Wilms tumor and have completed therapy for the tumor. I have read and understand the two-page explanation of the purpose of this research study, and of the potential risks and benefits of participation, which is attached to this consent form. To determine the long-term effects of the treatment which has been given to me, I will be evaluated once per year by my own physician or if I have no physician, by completing a brief questionnaire. This research study involves the completion of several forms requiring information about my family and my current state of health. Depending upon my health status, I may also be asked to allow copies of my medical records (to evaluate complications of previous treatment, childbirth, the occurrence of new medical conditions), and medical records regarding the birth and medical conditions of my children to be sent to the NWTS Data and Statistical Center. This study does not specifically involve obtaining any blood tests. These will be obtained at the discretion of my doctor.

POTENTIAL BENEFITS: Although there may be no direct benefit to me through participation in this study, other children who need treatment for Wilms tumor, the children's parents, and the health care professionals who take care of those children may benefit from increased knowledge about the children with Wilms tumor.

I understand that I will not be charged additional expenses for my participation in this study. I also understand that I will not receive money for participation in this study. I understand that I am free to withdraw my consent to participate in this study. I may withdraw consent at any time and this decision will not adversely affect my care at this institution or cause a loss of benefits to which I might be otherwise entitled.

All data obtained from this research will remain confidential and will only be used for biomedical research. The confidentiality of this document and all records from this research will be protected to the extent provided by law. Neither my name nor any other family member's name will be used in any report.

My signature below indicates that I have read all the above information, received answers concerning areas I do not understand, and am willingly giving my consent to participate in this program. On signing this form, I will receive a copy.

Patient

Date

Witness

Date

Physician

Date

LATE EFFECTS STUDY **CONSENT FORM PAGE 2: OVER 18 YEARS OF AGE** **ADULT CONSENT FORM**

You are being asked to continue participation in this study because you were previously treated for Wilms tumor on the NWT5-5 protocol. This research project includes only people who choose to take part in it. Please consider the following information and take your time in making your decision.

WHY IS THIS STUDY BEING DONE?

The Late Effects Study is being conducted in order to answer scientific questions and to serve as a resource for Wilms tumor patients and their families. Although most people in this study enjoy good health, some may be at risk for certain health conditions. We are collecting information from as many participants as possible in order to determine if they or their offspring are at risk for adverse medical conditions. If there is more than one case of Wilms tumor in a given family, we plan to work with geneticists to try to estimate heritability and recurrence risks. We would like to answer your questions about possible long-term effects of treatment for Wilms tumor. This is why we are collecting information on health issues and pregnancies.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Over 5,000 people have chosen to participate in this study. We expect that more people will enroll as we contact them to continue participation, at least 1,500 between December 2006 and November 2011.

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Every five years we will send a Medical History Form for you to fill out and a Physical Exam Form for your physician to complete and return. In each of the intervening four years we send an annual request. This Annual Status Report asks about significant health events and confirms your most recent address.

Reports of conditions of particular interest are followed up with requests for consent to obtain confirming medical records. Current conditions of interest include pregnancy in participant or partner, heart, kidney or lung conditions, the development of other cancers, and the diagnosis of Wilms tumor in a family member.

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WHAT IF I AM NOT SEEING A PHYSICIAN?

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ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to continue participation in this study you may not personally experience any medical benefits. However, you may benefit by the resources we provide when you contact us for information or advice. Members of our national committee stand ready to answer, as knowledgeably as possible, any questions you may have.

We believe that the information we collect about you and other participants will benefit other people diagnosed with or touched by Wilms tumor. Already people entered on the NWT5 protocols have contributed enormously to our ability to successfully treat a new generation of children with Wilms tumor. By continuing to gather information on your current health and the health of your children we hope to learn about any risks associated with treatment for Wilms tumor.

LATE EFFECTS STUDY **CONSENT FORM PAGE 3: OVER 18 YEARS OF AGE** **ADULT CONSENT FORM**

WHAT ARE THE RISKS OF THE STUDY?

We respect that each person has a different comfort level with sharing certain aspects of his or her medical history. This discomfort is the primary risk of participation. However, we ask that you let us know if there is a particular part of our study for which you would rather not provide information. When we ask for annual updates you may decline to provide answers or releases for medical records if you are uncomfortable in sharing this information. Please let us know if you do not want to answer a particular question.

HOW LONG WILL I BE IN THE STUDY?

We would like you to participate in this study until the research is completed. However, you may withdraw at any time. We hope that you decide to continue participating and help us with this important research. However, if you decide to withdraw your consent to participate in the study, we encourage you to talk to your regular doctor first and to retain the information in this document so that you may contact us in the future. We remain available to you as a resource regardless of your participation status.

WHAT ABOUT CONFIDENTIALITY?

Extensive efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality, but only those involved in the science of the study will be granted access to your medical records. Your personal identity will not be revealed in any publication or report.

In order to ensure compliance with the laws that govern research, the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board (IRB) will periodically audit studies. As part of their audit process, the IRB may review your medical records as they pertain to this protocol to ensure that the informed consent process was conducted properly. If you have any questions about this review process, you may call Karen Hansen, Director of the FHCRC Institutional Review Office at (206) 667-4867.

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WHOM DO I CALL FOR MORE INFORMATION OR IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study please call Dr. Norman Breslow at (800) 553-4878. Dr. Breslow is the Principal Investigator of the Late Effects Study, and the NWTs Statistician. You may also visit the website of the Data and Statistical Center at <http://www.nwtsg.org>.

LATE EFFECTS STUDY INFORMATION SHEET FOR INSTITUTIONS

PATIENT ID# «COOP_NUM» PATIENT NAME: «FRSTNAME» «LASTNAME»

DATE OF BIRTH: «D_BIRTH» DATE OF NWTS-5 REGISTRATION: «D_REGIS»

RELEASE AUTHORIZATION FORM: If a patient is no longer returning to your institution we ask that you submit a Release Authorization signed by the treating physician authorizing the Data and Statistical Center to contact the patient for follow-up directly.

FOLLOW-UP: Patients on study receive automated requests sent to the appropriate source. Forms are sent to the institution of record for patients remaining in follow-up by the institution, and directly to the family/patient for survivors released by the treating physician to direct follow-up. The one exception is the Flowsheet form, used by institutions. Flowsheets and all other forms may also be downloaded in PDF format from <http://www.nwtsg.org>.

YEARS SINCE DIAGNOSIS	DUE DATE	FORM(S) TO BE SUBMITTED
2	_____	Informed Consent, Flowsheets
3	_____	Flowsheets
4	_____	Flowsheets
5	_____	Physical Exam, FMHF/APMHF*
6	_____	Annual Status Report
7	_____	Annual Status Report
8	_____	Annual Status Report
9	_____	Annual Status Report
10	_____	Physical Exam, FMHF/APMHF*
11	_____	Annual Status Report
12	_____	Annual Status Report
13	_____	Annual Status Report
14	_____	Annual Status Report
15	_____	Physical Exam, FMHF/APMHF*
16	_____	Annual Status Report
17	_____	Annual Status Report
18	_____	Annual Status Report
19	_____	Annual Status Report
20	_____	Physical Exam, FMHF/APMHF*
21	_____	Annual Status Report
18 th birthday	_____	Adult Consent Form

HOW TO REACH US WITH QUESTIONS: If you have any questions please call the Data and Statistical Center in Seattle. You may leave a message at (800) 553-4878, or speak with a data coordinator during business hours by calling (206) 667-2967. Our web site answers Frequently Asked Questions and contains the email addresses of our staff: <http://www.nwtsg.org>.

* Family Medical History Form / Adult Patient Medical History Form

LATE EFFECTS STUDY INFORMATION SHEET FOR INSTITUTIONS

BEFORE REGISTRATION: Institutions should obtain IRB approval for the LATE Effects study, and submit a Patient Entry Questionnaire to the NWTS Data and Statistical Center (DSC) documenting approval. The PEQ form is available at <http://www.nwtsg.org/institutions.html>.

LATE EFFECTS STUDY REGISTRATION: Only NWTS-5 patients remain to be consented and registered on the NWTS Late Effects Study.

1. **If the NWTS-5 Informed Consent provided for long term follow-up, you may simply notify the Data and Statistical Center that you have obtained consent to register the patient.**
2. **If the NWTS-5 Informed Consent did not provide for long term follow-up, please forward the Family Information Packet to the family together with a consent form. Notify the DSC that you have obtained consent to register the patient.**
3. If the institution is not in periodic contact with the family, **a Release Authorization signed by the treating physician** will allow the Data and Statistical Center to contact the family directly. Immediate return of a Release Authorization will help avoid the loss of patients from continued follow-up. If an institution is unable to return a signed Release Authorization for any reason, please call the DSC immediately.

DATA SUBMISSION: Patients on study receive automated requests for follow-up sent to the appropriate source. The DSC sends all forms to the institution of record unless the DSC is in direct contact with the patient. Forms may also be downloaded in PDF format from <http://www.nwtsg.org>.

1. Medical History Forms are requested on 5th anniversaries following diagnosis. These should be given to the families for completion. Institutions are asked to not complete from information on file.

The Adult Patient Medical History Form (APMHF) is for patients who are 18 or older, while the Family and Medical History Form (FMHF) is sent to the parents of patients who are under 18.

2. NWTS Flowsheets should be submitted to document patient contact and to identify pregnancies or serious medical problems prior to the fifth anniversary following diagnosis.
3. NWTS Late Effects Study: Physical Examination (PE) is requested on fifth anniversaries. The current physician of record should complete this form.
4. NWTS Late Effects Study Annual Status Report (ASR) is requested starting on the sixth year following diagnosis, excluding 5th anniversaries. The current institution of record will complete this form for patients remaining in follow-up by the institution, or send it to the family for completion.

NWTS Adult Consent Form (ACF) is requested when a patient turns 18 years of age. This solicits informed consent for continued participation. The consent form, cover letter, and informational bulletin are sent to the institution. **If your institution is no longer in direct contact with the family please send a signed Release Authorization to the DSC.**

DATE _____

LATE EFFECTS STUDY ANNUAL STATUS REPORT (SENT TO FAMILY)

Participant Name: «PATIENTNAME»

NWTS #«NWTSID»

In order to maintain contact so that we may send the Physical Exam and the Medical History forms to you every five years for the above participant, we would like to have you complete and sign this status report at your earliest convenience and return it to us in the self-addressed, stamped envelope. If you would like to complete this report online, go to our website, www.nwtsg.org, and click on the SurveyMonkey link. Thank you for your continued participation in our study.

1. Has your name, address or telephone number changed? If so, please make corrections in the space provided.

«CONTACTNAME» _____

«ADDRESSA» _____

«ADDRESSB» _____

«CITYSTATEZIP» _____

<CONTPHON>, <CONTCELL> _____

Alternate phone # or email address? _____

2. Has <FIRSTNAME> had any serious illnesses or conditions resulting in hospitalization, surgery or other medical treatment since <date last seen>? If so, please use the space below to report each event.

Event	Date of Occurrence	Description/Outcome/Treatment
-------	--------------------	-------------------------------

3. **Since treatment ended or since your last report**, has <FIRSTNAME> experienced any significant life events such as marriage, pregnancy or parenthood? If yes, please use the space below to report each event.

Event	Date of Occurrence	Description/Outcome
-------	--------------------	---------------------

SIGNATURE: _____

Date: _____

Relationship to <FIRSTNAME>: _____

LATE EFFECTS STUDY: 5 YEAR ANNIVERSARY PACKET

DATE

TO: <DMNAME>, Data Manager(s)
<INSTNAME>

FROM: Data Coordinators

RE: <PATIENTNAME>
Patient ID #<PATIENT_ID>

<FIRSTNAME> was registered with the NWTS on <D_REGIS> and was last reported alive on <D_CLSEEN>. The NWTS Protocol stipulates that all patients surviving five years from diagnosis will have complete forms every 5 years from diagnosis. This patient's <ANNIVERSARY>th year anniversary will occur in the next few months.

Please find enclosed two study forms which are to be completed for the <ANNIVERSARY>th anniversary. If the patient has been examined by you in the past year please complete the Physical Examination form from your records and return it to us. Please also forward the Family and Medical History Form and the information sheet to the patient or family with instructions to return it either directly to the NWTS DSC or, if you prefer, to you for forwarding.

If you have not seen the patient within the past year, please schedule an examination for <FIRSTNAME> as soon as it is convenient. Both forms and the information sheet may be placed in the patient file so that these are available at the time of the examination. Please return both forms after the visit. The information sheet may be given to the family at that time.

FLWSHEETS CANNOT BE SUBSTITUTED FOR THE PHYSICAL EXAMINATION FORM.

If you are no longer seeing <FIRSTNAME> or have had no follow-up reported in the past two years we encourage you to please release this patient to direct follow-up through the DSC. This is accomplished by returning a completed and SIGNED Release form.

Each year we will contact you using the Annual Status Report to make sure that you are still providing follow-up for this patient. However, the two main study forms will only be sent to you at five year anniversaries.

Thank you for your cooperation in this important endeavor.

NWTS LATE EFFECTS STUDY: PHYSICAL EXAMINATION

I. PATIENT NAME: <PATIENTNAME> BIRTHDATE: <D_BIRTH> PATIENT ID #<PATIENT_ID>

Name of Physician Examining Patient: _____

Address: _____

Date of Exam: _____ Date/Cause of Death: _____

II. PHYSICAL FINDINGS: (Please indicate "ND" if not done)

Height (cm): _____ Weight (kg): _____ Blood Pressure: _____/_____

III TESTS ADMINISTERED: (Please indicate "ND" if a test was not done)

Chest X-ray: ()Not done ()Normal ()Abnormal (explain): _____

Other Imaging: ()Not done ()Normal ()Abnormal (explain): _____

Kidney Function: ()Not done ()Normal ()Abnormal (explain): _____

Liver Function: ()Not done ()Normal ()Abnormal (explain): _____

Cardiac Function: ()Not done ()Normal ()Abnormal (explain): _____

IV. PLEASE CHECK IF NORMAL AND DESCRIBE IF ABNORMAL. DO NOT LEAVE ANY CATEGORIES BLANK

SYSTEM	NORMAL	ABNORMAL	COMMENT
Hearing/Vision			
Skin/Hair/Nails			
Musculoskeletal			
Cardiovascular			
Pulmonary			
Gastrointestinal			
Hepatic			
Urinary (include infections)			
Neurologic			
Other (describe)			
Reproductive			

V. REPORT OF PREGNANCY IN NWTS PARTICIPANT OR PARTNER:

(In the instance of a multiple live birth please complete a report for each child)

Date Pregnancy Ended: _____ Duration (weeks): _____ Sex: _____ Weight: _____ Birth Order: _____

Outcome (e.g., single/multiple live birth, spontaneous abortion, please specify): _____

Note any complications or diseases during pregnancy: _____

Note any birth defects, diseases, or handicaps in the children: _____

Name of person completing form (please print): _____

SIGNATURE: _____ Date: _____

(Examining Physician)

Please mail the completed form to:
National Wilms Tumor Study, Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M2-A876, P.O. Box 19024, Seattle, WA 98109
Telephone: (206) 667-4842, Message Line: (800) 553-4878, Fax: (206) 667-6623

NWTS LATE EFFECTS STUDY FAMILY AND MEDICAL HISTORY FORM

Participant Name: <PATIENTNAME>
Birth Date: <D_BIRTH>
coded won't request> _____

Patient ID #<PATIENT_ID>
Last 4 Digits of Social Security # (Optional):<if already

I. PARENT DATA

FATHER (OR GUARDIAN 1)

MOTHER (OR GUARDIAN 2)

	1.	YES	NO		1.	YES	NO
1. Biological Parent? (circle one)	2.	_____		2.	_____		_____
2. Name (include maiden name)	3.	_____		3.	_____		_____
3. Birth Date	4.	<if already coded won't request>		4.	<if already coded won't request>		_____
4. Last 4 Digits of Social Security # (Optional)	5.	_____		5.	_____		_____
5. Current Address		(Street)			(Street)		_____
		(City, State, Zip Code)			(City, State, Zip Code)		_____
6. Phone Number	6.	()		6.	()		_____
7. Current Employer	7.	_____		7.	_____		_____
		(Name and type of business)			(Name and type of business)		_____
		()			()		_____
		(Phone Number)			(Phone Number)		_____
8. Serious Illnesses	8.	_____		8.	_____		_____
		_____			_____		_____
9. Deceased? (Cause/Date)	9.	_____		9.	_____		_____

II. <FIRSTNAME>'S MEDICAL HISTORY:

Since completion of treatment for Wilms tumor please report serious illnesses, hospitalizations, and second tumors if not previously reported to NWTS.

Date	Diagnosis	Hospital(City/State)	Physician	Treatment/ Outcome
------	-----------	----------------------	-----------	-----------------------

- 1.
- 2.
- 3.
- 4.
- 5.

(IF MORE THAN FIVE, PLEASE ADD A CONTINUATION PAGE)

III. <FIRSTNAME>'S SOCIAL HISTORY

We last received information about <FIRSTNAME> on <D_CLSEEN>. Since then, has <FIRSTNAME> experienced any significant events such as moving away from home, marriage, pregnancy or parenthood? If yes, please use the space below to report each event.

Event	Date of Occurrence	Description/Outcome
_____	_____	_____
_____	_____	_____
_____	_____	_____

FAMILY AND MEDICAL HISTORY FORM CONTINUED

PATIENT ID #<PATIENT_ID>

IV. <FIRSTNAME>'s SIBLINGS:

(Note half siblings with *, and indicate natural parent (mother/father) shared with <FIRSTNAME>.)

Full Name or "Still Born", etc.	Sex/ Birth Date	Serious Illnesses	Death: Date/Cause
1.			
2.			
3.			
4.			
5.			

(If more than five, please add a continuation page)

V. AUTHORIZATION AND CONTACT DATA

Currently we are receiving information about <FIRSTNAME> from her doctor. In the future, may we have your permission to contact you directly for this information? YES NO

 If yes, by phone? YES NO

 by mail? YES NO

Name: _____ Relationship to <FIRSTNAME>: _____

Address: _____

Phone Number: () _____

Please identify two individuals, (not living at your address), who should know <FIRSTNAME>'s whereabouts so if you move we can maintain contact with <FIRSTNAME>.

Name: _____ Relationship to <FIRSTNAME>: _____

Address: _____ Phone Number: () _____

Name: _____ Relationship to <FIRSTNAME>: _____

Address: _____ Phone Number: () _____

COMMENTS:

Signature of person completing this form: _____

Relationship to <FIRSTNAME>: _____ Date this Form Completed: _____

Please mail the completed form to:

**National Wilms Tumor Study, Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M2-A876, P.O. Box 19024, Seattle, WA 98109
Telephone: (206) 667-4842, Message Line: (800) 553-4878, Fax #: (206) 667-6623**

LATE EFFECTS STUDY ADULT CONSENT FORM

DATE

«PSALUTATION_FL»
c/o «DMNAME»
«INSTNAME»
«ADDRESSA»
«ADDRESSB»
«ADDRESSC»
«CITYSTATEZIP»

Patient ID #«PATIENT_ID»

Dear «PSALUTATION_L»:

I am the statistician for the National Wilms Tumor Study (NWTs). **Your parents consented for you to be enrolled in our study in «REGIS_YEAR»** when you were diagnosed with the rare childhood kidney disease known as Wilms tumor. Since then, we have received information on your progress from them and from the institution at which you were treated. You and other participants have contributed valuable information about the diagnosis and treatment of Wilms tumor. Today the number of surviving patients is increasing as the overwhelming majority of affected children are cured of their disease.

Now that you are 18 years or older, we are requesting your consent, as an adult, for the NWTs to continue to follow your progress. Accordingly, we are asking you to complete, sign, and return the enclosed Adult Consent Form to «INSTNAME» at your earliest convenience. In addition, if you would prefer that we contact someone else (i.e. your parent, spouse, etc.), please also indicate that on the enclosed form.

We are requesting your continuing participation in our study so that we may learn more about whether there are long term consequences of childhood cancer treatment. We are happy to make available to you, upon request, any published findings of the NWTs.

We have designed the study to cause you as little inconvenience as possible. We ask that the two forms we will send at five year intervals be filled out and returned to us. In the intervening years we will send you a brief annual mailing to make sure that we have your current address on file. If you or your spouse/partner become pregnant, or if you develop any serious medical problems, we may request additional information at that time. In addition, *some* participants may be contacted occasionally for special studies.

Please feel free to contact us at (800) 553-4878 or email nwtsg@fhcrc.org at any time if you have questions, would like a more detailed explanation of the NWTs, or would like to share any new information with us. **If you should decide to discontinue your participation,** check the second box on the form, sign and return it and we will send you no further correspondence. However, I certainly hope that you will decide to continue in this important study and return the completed adult consent form.

With many thanks for your past cooperation and best wishes for the future.

Yours sincerely,



Norman Breslow, Ph.D.
NWTs Statistician

January 26, 2010

LATE EFFECTS STUDY ADULT CONSENT FORM

1. I, «PATIENTNAME», (Patient ID # <PATIENT ID>), consent to participate in this study about my medical history and progress related to my treatment for Wilms Tumor (*using my contact information given directly below*).

Signed: _____ Date: _____

Full Name: _____

Address: _____

_____ Phone Number: _____

Last 4 digits of Social Security # (Optional): <if already coded won't request> _____

2. The people listed below (for example, parents, spouse, fiancé) may also report my health information to the NWTS (*optional*). This does not include permission to access my medical records.

Full Name: _____ Relationship: _____

Address: _____

_____ Phone Number: _____

Full Name: _____ Relationship: _____

Address: _____

_____ Phone Number: _____

Full Name: _____ Relationship: _____

Address: _____

_____ Phone Number: _____

If more than three, please continue on the back.

3. Please remove my name from your mailing list and discontinue contacting me about the National Wilms Tumor Study.

Signed: _____ Date: _____

I retained a copy of this form.

Please send me a copy of this form.

LATE EFFECTS STUDY ADULT CONSENT FORM

You are being asked to continue participation in this study because you were previously treated for Wilms tumor on a National Wilms Tumor Study protocol. This research project includes only people who choose to take part in it. Please consider the following information and take your time in making your decision.

WHY IS THIS STUDY BEING DONE?

The Late Effects Study is being conducted in order to answer scientific questions and to serve as a resource for Wilms tumor patients and their families. Although most people in this study enjoy good health, some may be at risk for certain health conditions. We are collecting information from as many participants as possible in order to determine if they or their offspring are at risk for adverse medical conditions. If there is more than one case of Wilms tumor in a given family, we plan to work with geneticists to try to estimate heritability and recurrence risks. We would like to answer your questions about possible long-term effects of treatment for Wilms tumor. This is why we are collecting information on health issues and pregnancies.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Over 5,000 people have chosen to participate in this study. We expect that more people will enroll as we contact them to continue participation, at least 1,500 between December 2006 and November 2011.

WHAT DOES PARTICIPATION INVOLVE?

Every five years we will send a Medical History Form for you to fill out and a Physical Exam Form for your physician to complete and return. In each of the intervening four years we send an annual request. This Annual Status Report asks about significant health events and confirms your most recent address.

Reports of conditions of particular interest are followed up with requests for consent to obtain confirming medical records. Current conditions of interest include pregnancy in participant or partner, heart, kidney or lung conditions, the development of other cancers, and the diagnosis of Wilms tumor in a family member.

We will always enclose return envelopes for your convenience.

WHAT IF I AM NOT SEEING A PHYSICIAN?

When we send the Physical Exam Form every five years we understand that a visit to a health care provider may be a prohibitive expense for some. Completion of this form is not a requirement for participation. Although we recommend continued medical care, we would like to continue hearing from you regardless of your ability to be seen by a health care provider.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to continue participation in this study you may not personally experience any medical benefits. However, you may benefit by the resources we provide when you contact us for information or advice. Members of our national committee stand ready to answer, as knowledgeably as possible, any questions you may have.

We believe that the information we collect about you and other participants will benefit other people diagnosed with or touched by Wilms tumor. Already people entered on the NWTS protocols have contributed enormously to our ability to successfully treat a new generation of children with Wilms tumor. By continuing to gather information on your current health and the health of your children we hope to learn about any risks associated with treatment for Wilms tumor.

LATE EFFECTS STUDY ADULT CONSENT FORM

WHAT ARE THE RISKS OF THE STUDY?

We respect that each person has a different comfort level with sharing certain aspects of his or her medical history. This discomfort is the primary risk of participation. However, we ask that you let us know if there is a particular part of our study for which you would rather not provide information. When we ask for annual updates you may decline to provide answers or releases for medical records if you are uncomfortable in sharing this information. Please let us know if you do not want to answer a particular question.

HOW LONG WILL I BE IN THE STUDY?

We would like you to participate in this study until the research is completed. However, you may withdraw at any time. We hope that you decide to continue participating and help us with this important research. However, if you decide to withdraw your consent to participate in the study, we encourage you to talk to your regular doctor first and to retain the information in this document so that you may contact us in the future. We remain available to you as a resource regardless of your participation status.

WHAT ABOUT CONFIDENTIALITY?

Extensive efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality, but only those involved in the science of the study will be granted access to your medical records. Your personal identity will not be revealed in any publication or report.

In order to ensure compliance with the laws that govern research, the Fred Hutchinson Cancer Research Center (FHCRC) Institutional Review Board (IRB) will periodically audit studies. As part of their audit process, the IRB may review your child's medical records as they pertain to this protocol to ensure that the informed consent process was conducted properly. If you have any questions about this review process, you may call Karen Hansen, Director of the FHCRC Institutional Review Office at (206) 667-4867.

WHAT ARE THE COSTS?

This study makes no payments to participants for taking part in the study. We are also unable to provide any money for medical examinations or treatment.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Again, you may contact Karen Hansen at the phone number above regarding your rights as a research participant.

WHOM DO I CALL FOR MORE INFORMATION OR IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study please call Dr. Norman Breslow at (800) 553-4878. Dr. Breslow is the Principal Investigator of the Late Effects Study, and the NWTs Statistician. You may also visit the website of the Data and Statistical Center at <http://www.nwtsg.org>.

Q9403
Appendix B

UNIVERSITY OF WASHINGTON
SEATTLE, WASHINGTON 98195

*School of Public Health and Community Medicine
Department of Biostatistics, Box 357232*

DATE

«ContactName»
«AddressA»
«AddressB»
«CITYSTATEZIP»

RE: Name: «PATIENTNAME»
Birthdate: «BIRTHDATE»
Reference number: «NWTSID»

Dear «Salutation»,

We represent a national medical study. **The person listed above, and her family, have participated in our study since <YEAR>.** We have been authorized by <INSTITUTION_OR_PI> to contact them. Lately we have been unable to reach them, and we would like to contact them to see if they are willing to continue their participation in our study. Could you help us get back into contact with them either by confirming that you are the correct party to contact or by forwarding this letter to the correct party to contact? ***Please be assured that we are not affiliated in any way to a credit, financial, or legal agency.***

If you do not know «FIRSTNAME» or her family, please let us know that as well so we do not continue to contact you in the future.

Please answer the questions below, and return this letter to us in the envelope provided. Any information that you provide will be held in strict confidence and used only by us for locating our study participants. If you prefer, you can leave a message 24 hours a day at 1-888-271-1407 or leave an email message at childrens_health_study@yahoo.com. Please leave your name, phone number and the reference number printed above and our data coordinator will return your call. Thank you very much for any assistance you may provide.

Contact Name: _____

Relationship to «FIRSTNAME»: _____

Address: _____

Phone: _____

Other Name/s to Contact (please specify if relative, friend, employer): _____

Address: _____

Phone: _____

Comments: (We would greatly appreciate being updated about «FIRSTNAME»'s health): _____

Sincerely,



Norman Breslow, Ph.D.
Statistician

January 26, 2010

PREGNANCY SURVEY

Participant Name: <PNAME> _____

NWTS # or Patient ID<ID#>

Many participants and their families have contacted us with questions about fertility and pregnancy. We very much want to answer these questions, so we need everyone's help to gather that important information. Preliminary information showed us that almost all survivors of Wilms tumor are capable of becoming parents. We are currently updating this study and need everyone's help in order to confirm that the earlier information continues to be true.

This survey is being sent to all participants, **males and females**. It is just as important for us to hear from female participants who have not become pregnant and male participants who have not fathered a child as it is to hear from participants or participants' partners who have had pregnancies. Reports of pregnancy will be followed up by our staff. We will send you a brief questionnaire about you or your partner's pregnancy and ask you to sign a medical records release.

We very much appreciate your cooperation in completing a comprehensive listing of you or your partner's pregnancies to make sure we have not missed any reports due to lapses in contact with you. Your reports should include all pregnancies regardless of outcome (full term and early deliveries, miscarriages, etc.). Thank you for your continued contribution.

Pregnancy	Date pregnancy ended or completed	Outcome: Full term, Still Born, Miscarriage, etc.
1	____/____/____	_____
2.	____/____/____	_____
3.	____/____/____	_____
4.	____/____/____	_____
5.	____/____/____	_____
6.	____/____/____	_____
7.	____/____/____	_____

I have no pregnancies to report

You have my permission to contact me in order to obtain further information about my medical history and progress related to my treatment for Wilms tumor

____/____/____
Date
(____) - ____ - ____

Signature

Telephone

Printed Name

Best time to call

Address

City, State, Zip

PLEASE COMPLETE THIS SURVEY AT YOUR EARLIEST CONVENIENCE AND RETURN IT TO US IN THE SELF-ADDRESSED STAMPED ENVELOPE PROVIDED.

NATIONAL WILMS TUMOR STUDY - PREGNANCY QUESTIONNAIRE

(TO BE FILLED OUT BY MOTHER OF CHILD, WHENEVER POSSIBLE)

Name of NWTS participant: «PATIENTNAME»

NWTS #«NWTSID» - «BTHORD»

1. You are: (Circle one)
a. The NWTS participant
b. The spouse/partner of NWTS participant (Please give your name): _____

2. Date pregnancy ended: ___/___/___

3. Duration of pregnancy (weeks): _____

4. Pregnancy outcome, please circle one of the following:
- | | |
|--------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| a. Single live birth * | f. Multiple live birth * (please circle birth order for the child described on this form: 1 2 3 and <u>include a separate questionnaire for each child</u>) |
| b. Stillbirth | g. Therapeutic abortion |
| c. Miscarriage | h. Other, please specify: _____ |
| d. Ectopic pregnancy | |
| e. Elective termination of pregnancy | |

* May we have your permission to request periodic follow-up on the health status of this child? (Circle one): YES NO

5. Hospital name where delivery or other care was performed: _____
Hospital address: _____ City/State/Zip: _____

6. Name of obstetrician/midwife: _____
Address: _____ City/State/Zip: _____

7. Weight of infant at delivery (lb./oz): _____ lbs. _____ ozs. Child's sex: _____

8. Child's full name as recorded on birth certificate: _____

9. Last 4 digits of Child's Social Security Number (Optional): _____

10. Child's mother's date of birth: _____ Child's father's date of birth: _____

11. Please note any birth defects, diseases or handicaps in your child and the date of diagnosis.

<u>Condition</u>	<u>Date of Diagnosis</u>	<u>Hospital (include city/state)</u>
_____	____/____/____	_____
_____	____/____/____	_____

12. Is this child now living? (Circle one): YES NO
If not: Date of death: ___/___/___ Cause of death: _____ City/State: _____

13. Please list any complications or diseases you had during this pregnancy:

14. Did you and your spouse/partner have difficulty becoming pregnant? (Circle one): YES NO
Comments: _____

15. We may contact you if we have more questions. Please provide your telephone numbers and email:

16. What is your preferred method of contact?: _____

Thank you for your cooperation in completing this form. We have provided a self-addressed, stamped envelope for your use.

Signed: _____ Date: _____

NATIONAL WILMS TUMOR STUDY - PREGNANCY RECORDS REQUEST
(SENT TO HOSPITAL/OBGYN CLINIC SIGNED BY DR. GREEN)

«OBGYN»
Medical Records / Release of Information Desk
«OBA1»
«OBA2»
«OBCStZip»

Dear Release of Information Desk:

We are requesting copies of selected medical records for «**MomFullN**» (**Date of Birth: «MDob»**). These are being requested in relation to her ongoing treatment and health, and we therefore request that they be provided without charge.

Your help is being requested because you provided health care to «**MomFirstN**» during her pregnancy. Please send **photocopies of her complete medical records**, including office visit notes, letters from consulting physicians, hospital reports, and laboratory, pathology and x-ray reports for the following period of care: **pre-natal through post-partum exams(s)**, («**BbyDoB**»).

Please send all copies to my staff at this specific address (do not address to me):

Attention: «DC», M2-A876
NWTS Data and Statistical Center
Fred Hutchinson Cancer Research Center
PO Box 19024
Seattle, WA 98109

A copy of the signed authorization for the release of «**MomFirstN**»'s records is enclosed. For your convenience we have provided a business reply label. If you have any questions regarding the study or this request, please call me at (901) 595-5915, or «DC» at (206) 667-«DCphone». Collect calls are accepted. Your cooperation will be greatly appreciated.

Sincerely yours,



Daniel M. Green, MD

January 26, 2010

NATIONAL WILMS TUMOR STUDY - PREGNANCY RECORDS REQUEST
(SENT TO HOSPITAL/OBGYN CLINIC SIGNED BY DR. GREEN)

«Hosp»
Medical Records / Release of Information Desk
«HospA1»
«HospA2»
«HCStZip»

Dear Release of Information Desk:

We are requesting copies of selected medical records for «**MomFullN**» (**Date of Birth: «MDob»**). These are being requested in relation to her ongoing treatment and health, and we therefore request that they be provided without charge.

Your help is being requested because you provided health care to «**MomFirstN**» during her pregnancy. Please send **photocopies of her complete medical records**, including office visit notes, letters from consulting physicians, hospital reports, and laboratory, pathology and x-ray reports for the following period of care: **admission to discharge, («BbyDoB»)**.

Please send all copies to my staff at this specific address (do not address to me):

Attention: «DC», M2-A876
NWTS Data and Statistical Center
Fred Hutchinson Cancer Research Center
PO Box 19024
Seattle, WA 98109

A copy of the signed authorization for the release of «**MomFirstN**»'s records is enclosed. For your convenience we have provided a business reply label. If you have any questions regarding the study or this request, please call me at (901) 595-5915, or «DC» at (206) 667-«DCphone». Collect calls are accepted. Your cooperation will be greatly appreciated.

Sincerely yours,



Daniel M. Green, MD

January 26, 2010

NATIONAL WILMS TUMOR STUDY - PREGNANCY RECORDS REQUEST
(SENT TO HOSPITAL/OBGYN CLINIC SIGNED BY DR. GREEN)

«Hosp»
Medical Records / Release of Information Desk
«HospA1»
«HospA2»
«HCStZip»

Dear Release of Information Desk:

We are requesting copies of selected medical records for «BbyFullN» (**Date of Birth: «BbyDoB»**). These are being requested in relation to her/his ongoing treatment and health, and we therefore request that they be provided without charge.

Your help is being requested because you provided health care to «BbyFullN» during the time period for which we are interested in the medical history. Please send **photocopies of «BbyFirstN»'s complete medical records from birth («BbyDoB») to discharge** including office visit notes, letters from consulting physicians, hospital reports, and laboratory, pathology and x-ray reports.

Please send all copies to my staff at this specific address (do not address to me):

Attention: «DC», M2-A876
NWTS Data and Statistical Center
Fred Hutchinson Cancer Research Center
PO Box 19024
Seattle, WA 98109

A copy of the signed authorization for the release of «BbyFirstN»'s records is enclosed. For your convenience we have provided a business reply label. If you have any questions regarding the study or this request, please call me at (901) 595-5915, or «DC» at (206) 667-«DCPHONE». Collect calls are accepted. Your cooperation will be greatly appreciated.

Sincerely yours,



Daniel M. Green, MD

January 26, 2010

ANNUAL STATUS REPORT FOR YOUR CHILD(REN)

Participant Name: <PATIENTNAME>

NWTS #<NWTSID>

The NWTS has developed several treatment regimens since 1969 for the treatment of Wilms tumor and other kidney tumors of children. All of the regimens have been very effective for preventing the recurrence of kidney tumor, either in the original tumor site or at other sites in the body. To help us determine which treatment regimen should be used in future patients, we need to know the side effects of the treatment. One important group of side effects are those on the fertility of our participants and the health of their children. To determine these effects, we would like to receive updates on the health of all of your children. We appreciate your help with this effort very much.

While we believe it is unlikely that children of Wilms tumor survivors are at increased risk for the thirteen rare conditions listed below, it is important for us to identify if any have developed. For each child identified below by birth date please note if any of these conditions have been diagnosed. For some reports we may ask your permission to obtain copies of medical records.

Wilms tumor

Hypospadias (urethra where urine exits is angled differently – males only)

Sarcoma (bone or soft tissue cancer)

Congenital heart defect (problem with heart that you are born with)

Denys-Drash syndrome (kidney failure problem you are born with)

Cryptorchism (testicles are not descended into scrotal sac and need surgery to have them placed there)

Germ cell tumor (cancer of the reproductive organs, but can also be at the base of the spine or in the chest)

Aniridia (born without iris in the eye)

Polycystic disease of the kidney (fluid sacs in the kidneys causing them not to work right)

Hemihypertrophy (one side of any part of the body noticeably larger than the other)

Shortened limbs (arms or legs that are shorter than they should be)

Beckwith-Wiedemann syndrome (large tongue, low blood sugar at birth and malformed belly button or wall of belly)

Turner's syndrome (short, wide neck, abnormal ovaries girls can be born with – one X chromosome is missing in the cells)

If one or more of your children are not listed below, please update the list with each birth date. Also, please note other health conditions of importance, not listed above, for each child.

Child's Birth Date	Event/Date	Description/Outcome	Nothing to Report <input checked="" type="checkbox"/>
<BIRTH DATE CHILD 1>			<input type="checkbox"/>
<BIRTH DATE CHILD 2>			<input type="checkbox"/>
<BIRTH DATE CHILD 3>			<input type="checkbox"/>
<BIRTH DATE CHILD 4>			<input type="checkbox"/>
<BIRTH DATE CHILD 5>			<input type="checkbox"/>

SIGNATURE: _____

Date: _____

**NATIONAL WILMS TUMOR STUDY - MEDICAL RELEASE OF RECORDS REQUEST
(TO FOLLOW UP ON CONDITION REPORTED IN OFFSPRING)**

«CONTACTNAME»
«ADDRESSA»
«ADDRESSB»
«CITYSTATEZIP»

Dear «SALUTATION»:

Thank you for returning our <Annual Status Report for Your Child(ren) form> / <Pregnancy forms(s)> for your child born on <DATE>. As you know, we are following both participants and their children to help us determine which treatment regimen should be used in future patients, and to determine if there are any long-term side effects of the treatment in the participant or their children.

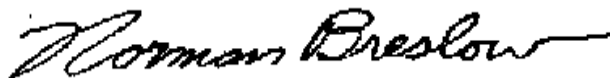
<You reported that <HE/SHE> has been diagnosed with <CONDITION>> / <When we received <HIS/HER> records from <Hospital Name>, we noted that <HE/SHE> was reported to have <CONDITION>>. This is a condition of interest to us, and we are requesting your permission to obtain copies of medical records documenting this diagnosis. We need your signed permission to contact the treating doctor(s) and hospital of record in order to obtain these.

I have enclosed <an> / <two> authorization form<s> for you to complete and sign. Please return them in our enclosed reply envelope. <Please provide the name of the pediatrician and any consultant(s) who diagnosed or followed-up on this condition.>

Please feel free to contact «DSCNAME» at any time if you have questions, would like a more detailed explanation of the NWTS, or would like to share any new information with us. You can leave a message anytime at 1-800-553-4878. Leave your name, phone number (including area code) and the best time to reach you and someone will return your call.

As always, your participation in this study is greatly appreciated. Thank you in advance for taking the time and interest to complete and return this form.

Sincerely,



Norman Breslow, Ph.D.
NWTS Statistician

January 26, 2010

AUTHORIZATION FOR RELEASE OF MEDICAL INFORMATION

for Name: <<OFFSPRING_NAME>> Birth Date: <<D PRGEND>> NWTS #<NWTSID> - <BTHORD>

For research purposes, I hereby authorize the release of medical records for documentation of a diagnosis of «**CONDITION**» which occurred on or about <DX_DATE>. If there was a hospitalization or outpatient visit which occurred around this date, I authorize the release of the <clinical reports>/<REPORT_REQ> **documenting the diagnosis, and copies of all other records related to the diagnosis and/or treatment of this condition.**

I understand that all information obtained will be held strictly confidential and will be used for statistical purposes only.

This authorization will be effective for two years from the date of signature and may be cancelled by me in writing at any time. A photocopy of this authorization will be treated in the same manner as the original.

Please sign both pages.

THE FOLLOWING IS TO BE COMPLETED BY THE PARENT/GUARDIAN

Date: ____/____/____ Last 4 digits of <CFNAME>'s Social Security # (optional): ____

Parent or Guardian's Signature: _____

Relationship to <CFNAME>: _____

Other names <CFNAME>'s records may be listed under: _____

Please list all doctors who have treated <<CFNAME>> for <<CONDITION>>.

1. Doctor who first diagnosed <<CONDITION>>:

Name of Doctor: _____ Telephone #: _____

Hospital or Clinic affiliation, if any: _____

Hospital or Doctor's address: _____

City/State/Zip: _____

2. Consultant or doctor who treated <<CONDITION>>:

Name of Doctor: _____ Telephone #: _____

Hospital or Clinic affiliation, if any: _____

Hospital or Doctor's Address: _____

City/State/Zip: _____

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Appendix C

3. Other doctors who have been involved in the diagnosis or treatment of <<CONDITION>>:

Name of Doctor: _____ Telephone #: _____

Hospital or Clinic affiliation, if any: _____

Hospital or Doctor's Address: _____

City/State/Zip: _____

Name of Doctor: _____ Telephone #: _____

Hospital or Clinic affiliation, if any: _____

Hospital or Doctor's Address: _____

City/State/Zip: _____

Name of Doctor: _____ Telephone #: _____

Hospital or Clinic affiliation, if any: _____

Hospital or Doctor's Address: _____

City/State/Zip: _____

Name of Doctor: _____ Telephone #: _____

Hospital or Clinic affiliation, if any: _____

Hospital or Doctor's Address: _____

City/State/Zip: _____

For research purposes, I hereby authorize the release of medical records for documentation of the diagnosis of <CONDITION>.

Parent or Guardian's Signature: _____

Relationship to <CFNAME>: _____

Date: ____/____/____

NATIONAL WILMS TUMOR STUDY - RECORDS REQUEST
(SENT TO HOSPITAL TO REQUEST DOCUMENTATION OF CONDITION REPORTED IN OFFSPRING)

DATE

«Hosp»
Medical Records / Release of Information Desk
«ADDRESSA»
«ADDRESSB»
«CITYSTATEZIP»
«HospCountry»

Dear Release of Information Desk:

We are requesting copies of selected medical records for «OFFSPRING_NAME» (Date of Birth: «D_PRGEND»). These are being requested for a research study, and we therefore request that they be provided without charge.

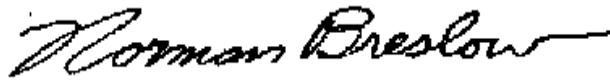
«CFNAME» was reported to have been diagnosed with «Condition». Your help is being requested because you provided health care to «CFNAME» during the period in which we are interested.

We are requesting photocopies of <clinical>/«Report_Req» report(s). Copies of the authorization forms signed by «CFNAME»'s parent are enclosed. For your convenience we have provided a business reply label.

If you have any questions regarding the study or this request please call «DSCName» at (800) 553-4878, and press <#> to leave a message. Leave your name, telephone number including area code, reference #«NWTSID»-«BTHORD» and the best time to reach you and we will return your call.

Many thanks for your assistance.

Yours sincerely,



Norman Breslow, Ph.D.
NWTS Statistician

January 26, 2010

NATIONAL WILMS TUMOR STUDY - FAMILIAL COVER LETTER
(SENT TO FAMILY REQUESTING HELP CONFIRMING POSSIBLE WILMS TUMOR IN A RELATIVE)

«CONTACTNAME»
«ADDRESSA»
«ADDRESSB»
«CITYSTATEZIP»

Dear «SALUTATION»:

I am the statistician for the National Wilms Tumor Study. You consented for <PNAME> to be enrolled in our study in «YR_REGIS» when he was diagnosed with the rare childhood kidney disease known as Wilms tumor. Since that time we have received a report on a family history form that his «RELATION» may have also been treated for kidney cancer. We are attempting to obtain clinical confirmation for an important study of familial Wilms tumor.

Families with more than one case of Wilms are of special interest to the NWTS. By studying families like yours we are attempting to determine the extent to which predisposition to the tumor is inherited and, eventually, to help identify children who might be at higher risk for the disease.

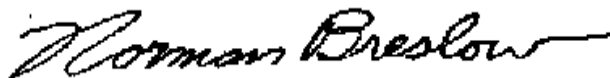
We hope that you will assist us in this study. Please forward the enclosed materials to the relative diagnosed with Wilms Tumor, or her/his guardian/closest living relative. The letter requests their permission to confirm the diagnosis. Information obtained is held in the strictest confidence, and only those directly involved in the science of the study will have access to it.

If you know for certain that this relative did not have Wilms tumor, or if this information is unavailable to you or your family please let us know and we will not continue to request this data.

Please feel free to contact us at any time if you have questions, would like a more detailed explanation of the NWTS, or would like to share any new information with us. You can leave a message anytime at 1-800-553-4878. Leave your name, phone number (including area code) and the best time to reach you and someone will return your call.

Thank you in advance for your assistance in this matter.

Sincerely,



Norman Breslow, Ph.D.
NWTS Statistician

January 26, 2010

**NATIONAL WILMS TUMOR STUDY - FAMILIAL COVER LETTER
(TO EXTENDED FAMILY REQUESTING MEDICAL RELEASE TO CONFIRM FAMILIAL WT)**

Dear Family Member of NWTS Participant:

We are asking «CONTACTNAME» to forward this letter to you regarding our study. «PNAME» was enrolled in the National Wilms Tumor Study (NWTS) in «YR_REGIS» when she was treated for Wilms tumor. Since that time we have received notice on a family history form that another family member may have also been treated for Wilms tumor. We would like to obtain clinical confirmation for our study. This packet has been forwarded to you in the belief that a member of your immediate family was diagnosed with kidney cancer.

Families with more than one case of Wilms are of special interest to the NWTS. By studying families like yours we are attempting to determine the extent to which predisposition to the tumor is inherited and, eventually, to help identify children who might be at higher risk for the disease.

If you or a member of your immediate family were diagnosed with Wilms and if you wish to participate please sign and return the enclosed release forms. Doing this gives us your permission to obtain the dates of treatment, the names of the hospital and doctor(s), and your consent for us to contact them to confirm the diagnosis of Wilms tumor.

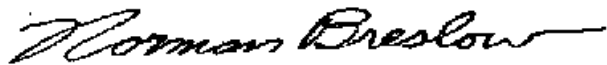
If you are willing to be contacted in order to learn more about our study before making a decision, please note your name and contact information on the back of this letter and return it to us in the enclosed business reply envelope. **Returning this letter and giving us permission to contact you directly does not mean you are agreeing to participate in the study.** Once the study has been described to you and we have answered any questions you may have, you will be invited to participate and you can choose at that time to participate or not.

If you do not wish to participate or if a member of your immediate family was not diagnosed with this condition, please note this on the back of this letter so that we do not continue to request this information in the future.

Please feel free to contact us at any time if you have questions, would like a more detailed explanation of the NWTS, or would like to share any new information with us. You can leave a message anytime at 1-800-553-4878. Leave your name, phone number (including area code) and the best time to reach you and someone will return your call.

Thank you in advance for your assistance in this matter.

Sincerely,



Norman Breslow, Ph.D.
NWTS Statistician

January 26, 2010

NATIONAL WILMS TUMOR STUDY
(SIGNED BY EXTENDED FAMILY TO ALLOW CONFIRMATION OF FAMILIAL WT)

AUTHORIZATION TO CONTACT HOSPITAL/PHYSICIAN

I authorize the staff at the National Wilms Tumor Study to contact

Hospital/Physician name

in order to secure further information about: _____'s
Name of Individual

diagnosis and treatment for Wilms tumor.

PERTINENT INFORMATION:

Date of Birth

Date of Treatment/Diagnosis of Wilms tumor

Other name(s) subject's records may be listed under

HOSPITAL WHERE DIAGNOSIS WAS MADE:

PHYSICIAN:

Hospital Name

Physician Name

Street Address

Street Address

City, State, Zip Code

City, State, Zip Code

(_____)_____
Phone Number

(_____)_____
Phone Number

I hereby authorize the release of all these hospital and physician records to Dr. Norman Breslow, Fred Hutchinson Cancer Research Center, Seattle, Washington.

I understand that all information obtained will be held strictly confidential and will be used for statistical purposes only.

This authorization will be effective for two years from the date of signature and may be cancelled by me in writing at any time. A photocopy of this authorization will be treated in the same manner as the original.

Signature of Subject
(or Legal Guardian, if applicable)

Relationship to Subject

Date Signed

January 26, 2010

**NATIONAL WILMS TUMOR STUDY
(LETTER REQUESTING AUTHORIZATION TO CONFIRM REPORT OF TARGETED LATE CONDITION)**

«ContactName»
«AddressA»
«AddressB»
«CityStateZip»
«Country»

Dear «Salutation»,

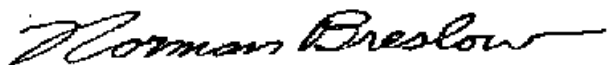
An important aspect of the National Wilms Tumor Study (NWTS) Late Effects Study is to identify any medical conditions that study participants may have had as a result of treatment for Wilms tumor. <I understand that you had a relapse of Wilms tumor that we were not previously informed of. It is important that we document your relapse and the treatment that you received for it. This information will help us put any late effects that you may experience in the proper context.>

In order to further the goals of our study and to follow up on the information we received from you, we would be most appreciative if you would take the time to complete the enclosed authorization forms, and return them to us in the self-addressed, stamped envelope. Then, with your permission, we will use the release to obtain the medical records documenting the diagnosis <and treatment> of <relapsed Wilms tumor in <YR_of_Relapse_Wilms>>/«Name_of_Condition» which you have reported to us.

Our current efforts are intended to update earlier studies in order to possibly improve or reduce treatment in newly diagnosed Wilms tumor patients as well as to alert study participants to problems that might possibly develop as a result of their treatment. Your assistance with this aspect of the study will be invaluable. Please don't hesitate to contact <DSCNAME> at (206) 667-<EXT> if you have any questions or concerns.

With many thanks for your continued participation in this important study.

Yours sincerely,



Norman Breslow, Ph.D.
NWTS Statistician

Encls.

January 26, 2010

AUTHORIZATION FOR RELEASE OF MEDICAL INFORMATION

For research purposes, I hereby authorize the release of medical records for documentation of a diagnosis of <relapsed Wilms tumor>/«**Reported Condition**» which occurred on or about _____/_____/_____ (mm/dd/yy).

If there was a hospitalization or outpatient visit which occurred around this date, <please provide copies of the operative and pathology reports for any surgical procedures as well as a summary of any chemotherapy and/or radiation therapy given as treatment for this relapse.>/<please provide a copy of the **pathology report** documenting the diagnosis.> / <I authorize a copy of all the following records that are available:

- Discharge summary from hospital
- Report of EKG
- Report of MUGA Scan
- Path report on any biopsy done
- Report of chest x-ray>/<I authorize a copy of all the following records that are available:
- Discharge summary from hospital**
- Reports of BUN, creatinine, urinalysis**
- Path report on any biopsy done**
- Report of late nephrectomy**
- Report of use of renal dialysis**
- Report of renal transplantation**

I understand that all information obtained will be held strictly confidential and will be used for statistical purposes only.

This authorization will be effective for two years from the date of signature and may be cancelled by me in writing at any time. A photocopy of this authorization will be treated in the same manner as the original.

Hospital or clinic where diagnosis was made: _____

Hospital or clinic address: _____ City/State/ZIP: _____

Name of physician: _____

Address: _____ City/State/ZIP: _____

Name of NWTS participant: <PATIENTNAME>, NWTS # <NWTSID>

_____/_____/_____
Birth Date

Last 4 digits of Social Security # (Optional)

Other names records may be listed under

Authorizing Signature

_____/_____/_____
Relationship to participant (parent, guardian, etc.) Date

**NATIONAL WILMS TUMOR STUDY
(LETTER REQUESTING DOCUMENTATION FOR TARGETED LATE CONDITION)**

<DATE>

<HOSPITAL>
Medical Records / Release of Information Desk
<ADDRESSA>
<ADDRESSB>
<<CITYSTATEZIP>>

Dear Release of Information Desk:

<PATIENTNAME> is a participant in the National Wilms Tumor Study, a cooperative program established in 1969 to study the treatment and long term outcome of patients with this rare childhood kidney tumor. This study includes the possible health effects of cancer and its treatment. Our NIH Award Number is 5R01 CA54498.

An important part of this study is the verification of medical information related to conditions reported in participants. Your help is being requested because you provided health care to <FIRSTNAME> during the time period for which we are interested in the medical history.

We are requesting photocopies of the **clinical reports documenting the diagnosis of <CONDITION>** which already has been reported to us by the participant. A copy of the signed authorization for the release of <FIRSTNAME>'s records is enclosed. For your convenience we have provided a self-addressed, stamped return envelope.

If there is a problem in providing the requested documentation, please call <DSC_NAME> at (206) 667-
<EXT> so that we can work together to solve the problem. Thank you very much for your help.

Yours sincerely,



Norman Breslow, Ph.D.
NWTS Statistician

Encls.

January 26, 2010