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CHILDREN'S ONCOLOGY GROUP

AREN0532

Treatment for Very Low and Standard Risk Favorable Histology Wilms Tumor

A Groupwide Phase III Study

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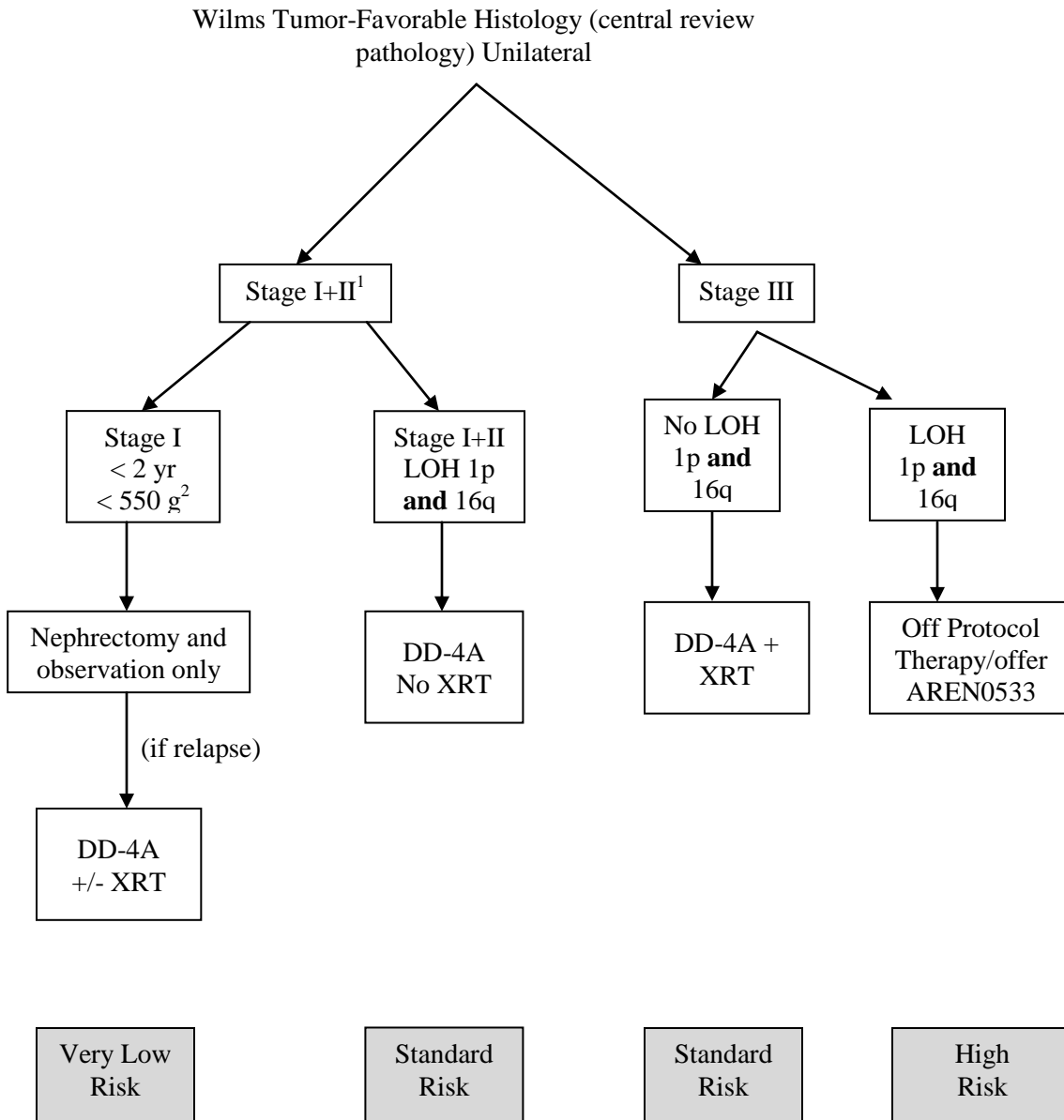
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ABSTRACT

AREN0532 is a COG protocol for patients up to age 30 years with Stage I-III favorable histology (FH) Wilms tumor stratified by clinical and biological risk factors. The overarching goal of this study is to provide a high degree of overall survival while minimizing toxicity. Previous work has shown that Stage I FH Wilms tumor, weighing less than 550 g in children less than 2 years of age, may be effectively treated as very low risk by surgery alone. Although the overall outcome for low risk FH Wilms tumor is good, some patients with apparently favorable clinical staging characteristics will relapse. Loss of heterozygosity (LOH) for chromosome 1p **and** 16q in Stage I and II FH Wilms tumor has been shown to be associated with a poorer prognosis. These patients will be moved from being treated with low risk chemotherapy while being observed on AREN03B2 to a standard risk arm and treated with the same chemotherapy as patients with Stage III Wilms tumor without LOH 1p **and** 16q. This study will have three strata: very low risk patients treated with surgery and observation alone, standard risk patients with LOH treated with dactinomycin, doxorubicin and vincristine, and standard risk patients treated with dactinomycin, vincristine and doxorubicin and radiotherapy.

EXPERIMENTAL DESIGN



Notes:

1. Stage I and II patients without combined LOH 1p and 16q will be followed on AREN03B2.
2. Must have had lymph node sampling at the time of nephrectomy to be eligible for this arm.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objective(s)

1.1.1 Objectives for Very Low Risk Favorable Histology, Wilms tumor

To demonstrate that very low risk patients treated by nephrectomy and observation alone will have a 4 year Event Free Survival of $\geq 85\%$ and 4 year Overall Survival $\geq 95\%$; very low risk is defined Stage I favorable histology tumors of weight < 550 g with patient age < 2 years at diagnosis.

1.1.2 Objectives for Standard Risk Favorable Histology Wilms tumor

To document continued excellent outcome (4 year Event Free Survival $\geq 85\%$ and Overall Survival $\geq 95\%$) for patients with Stage III favorable histology Wilms Tumor without LOH of 1p **and** 16q treated with vincristine, dactinomycin + doxorubicin + radiotherapy (Regimen DD-4A).

1.2 Secondary Objective(s)

1.2.1

To improve the current 4 year Event Free Survival for patients with Stage I and II Favorable Histology Wilms tumor with LOH of 1p **and** 16q by adding doxorubicin but not radiotherapy (modified Regimen DD-4A) to the standard dactinomycin and vincristine backbone.

1.2.2

To determine whether the omission of adjuvant therapy increases the incidence of contralateral kidney lesions in very low risk patients treated by nephrectomy and observation only.

1.2.3

To determine whether the omission of adjuvant therapy increases the incidence of renal failure in the very low risk patients that have metachronous relapse.

1.2.4

To monitor the outcomes for these very low and standard risk subsets of Favorable Histology Wilms tumors for correlation with biological data generated from the study of the tissues collected from these same cases on AREN03B2.

2.0 BACKGROUND

2.1 Rationale for Selected Approach and Trial Design

The overarching goal for children with Favorable Histology Wilms tumor (FHWT) is to more specifically target intensity of therapy to achieve a high degree of event free survival and overall survival while minimizing toxicity by utilizing a combination of biological and staging characteristics. This protocol will study elimination of exposure to upfront chemotherapy by patients with very low risk disease, and increased intensity of chemotherapy for those with newly validated biological features that suggest a higher risk of relapse despite historically good risk characteristics.

The majority of patients in this study will be treated with established standard chemotherapy regimens with proven excellent outcome from previous National Wilms Tumor Study (NWTS) studies. Outcomes of these patients will be tracked through minimal data collection for the main purpose of correlating clinical outcome with biologic variability and putative prognostic markers of Wilms tumor. Minimal data collection will include the following items: assigned treatment regimen, relapse, cause of death, and Grade IV toxicity. Follow up will be for five years following the last enrollment. Participation in the

tumor classification and biology study (AREN03B2) is mandatory for participation in this trial to ensure appropriate treatment stratification and to obtain samples for future validation of potential prognostic factors.

Tumor-specific Loss of Heterozygosity (LOH) for specific chromosomes has been explored as a potential prognostic factor in Wilms tumor. In an analysis of 232 Wilms tumor patients, preliminary data showed that tumor-specific loss of 16q occurred in 20% of patients and was associated with a poorer two-year Relapse Free survival (RFS) and Overall Survival (OS). Similarly, LOH for chromosome 1p was seen in approximately 11% of Wilms tumors and was also associated with poorer outcome of borderline significance. The fifth NWTS addressed the hypotheses that LOH 16q and/or 1p predict clinically significantly worse relapse-free survival and was designed to test this hypothesis within each Stage of FH disease. The results of NWTS 5 patients registered and followed to December 31, 2001 are shown below (Table 1):

Table 1. Outcomes by LOH (favorable histology Wilms tumor, all stages)

	LOH	#Pts	# Relapses	% 4 yr RFS	RR relapse	p value
1p	Loss	195	37	79.9	1.56	0.01
	None	1529	198	86.2	1.0	
16q	Loss	301	58	79.9	1.49	0.01
	None	1423	177	86.7	1.0	

These data show that tumor-specific LOH for either chromosome 1p or 16q is associated with an adverse outcome in favorable histology Wilms tumors, relative to those without LOH, although the association is stronger for LOH 1p. Outcomes by LOH 1p within each Stage are shown in the table below (Table 2).

Table 2. Outcome by LOH 1p and Stage, favorable histology only

Stage	LOH Status (1p)	# pts	Relapse-free Survival			Overall Survival		
			# relapses	4 yr RFS%	RR(95% C.I.) P-value	# deaths	4 yr OS%	RR(95% C.I.) P-value
I/Age<24m/Wt<550g								
	Loss	10	1	90.0	2.42(0.30-19.7)	1	90.0	16.5(1.03-264.0)
	Retain	162	7	95.6	P=0.41	1	100.0	p=0.047
I/Age>=24m or Wt>=550g								
	Loss	22	2	89.7	1.96(0.43-8.83)	3	82.4	10.0(2.01-49.4)
	Retain	221	11	94.2	P=0.38	4	98.4	p=0.005
II								
	Loss	74	19	72.9	2.21(1.32-3.69)	4	94.0	2.21(0.71-6.85)
	Retain	481	61	86.2	P=0.003	12	97.7	p=0.17
III								
	Loss	71	9	86.3	0.94(0.47-1.89)	4	94.5	1.1(0.38-3.21)
	Retain	417	57	86.5	P=0.86	21	94.4	p=0.86
IV								
	Loss	15	6	59.3	2.07(0.88-4.89)	3	73.8	1.46(0.44-4.86)
	Retain	183	40	76.4	P=0.10	24	86.1	p=0.53
V								
	Loss	3	0	100.0	0.0(----)	0	100.0	0.00(----)
	Retain	65	22	64.8	P=0.73	8	87.1	p=0.85
Total								
Total (stratified by above categories)	Loss	195	37	79.9	1.56(1.09-2.22)	15	91.2	1.84(1.05-3.24)
	Retain	1529	198	86.2	P=0.01	70	95.3	p=0.03

These results indicate that tumor-specific LOH 1p is associated with a significantly worse relapse free survival for Stage II patients but not apparently for Stage III/IV. This suggests that the adverse effect of LOH 1p may be overcome by the addition of more aggressive chemotherapy used for the more advanced stage tumors. The data show the same patterns for LOH 16q albeit with lower magnitude of relative risks. Finally, all the results shown above classify tumors by LOH for 1p or 16q. Although the study was not powered to examine the effect of the combination of LOH 1p and 16q, at least not within each stage, the results are revealing as shown below in the tables (Tables 3 and 4) below.

Table 3. Analysis for the joint effect of LOH 1p and LOH 16q for Stage I/II patients with FH

LOH Status	# pts*	Relapse-free Survival			Overall Survival		
		# relapses	4 yr RFS%	RR(95% C.I.) P-value**	# deaths	4 yr OS%	RR(95% C.I.) P-value**
Neither	750	60	91.2	-----	14	98.4	-----
1p only	60	11	80.4	2.19(1.15-4.17) p=0.02	4	91.2	4.03(1.20-12.43) p=0.02
16q only	114	19	82.5	1.91(1.14-3.21) p=0.01	3	98.1	1.40(0.40-4.95) p=0.60
Both	46	11	74.9	2.88(1.51-5.49) p=0.001	4	90.5	4.25(1.37-13.19) p=0.01

Table 4. Analysis for the joint effect of LOH 1p and LOH 16q for Stage III/IV patients with FH

LOH Status	# pts	Relapse-free Survival			Overall Survival		
		# relapses	4 yr RFS%	RR(95% C.I.) P-value*	# deaths	4 yr OS%	RR(95% C.I.) P-value*
Neither	500	82	83.0	-----	38	91.9	-----
1p only	56	6	89.0	0.69(0.30-1.57) p=0.37	2	97.6	0.52(0.12-2.14) p=0.36
16q only	100	15	85.3	0.89(0.51-1.54) p=0.67	7	92.0	0.88(0.39-1.97) p=0.76
Both	30	9	65.9	2.41(1.20-4.82) p=0.01	5	77.5	2.66(1.04-6.82) p=0.04

The effect of combined LOH on Favorable histology Stage III Wilms tumor alone is presented in table 5 demonstrating the effect on EFS and OS. There were 571 patients with Stage III FH Wilms tumor on NWT5 in the studied category for which 471 had adequate LOH data.

Table 5. Effect of combined LOH 1p **and** 16 q on outcome for Stage III FH Wilms tumor.

Patient subset Stage III FH	n of patients	5-year EFS	5-year OS
1p-/16q-	340	84%	95%
1p-/16q+	64	85%	92%
1p+/16q-	44	93%	95%
1p+/16q+	23	70%	89%

These data strongly show that the adverse prognosis in terms of relapse and death for Stage I, II and III disease is associated with LOH for both 16q **and** 1p. Patients with Stage I or II FH tumors with LOH for chromosome 1p will not have therapy intensified to the standard risk group (DD-4A – vincristine, dactinomycin, and doxorubicin). The rationale for this is that the significance of LOH 1p as a prognostic factor was not consistent across stages and is therefore of questionable importance. It is therefore harder to expose this group to potential toxicity by the addition of doxorubicin, in particular as the Overall Survival is not significantly different for Stage II patients with LOH 1p. We plan to continue to follow this potential prognostic factor through the AREN03B2 study.

Since recurrences in patients with LOH 1p **and** 16q occurred equally in the abdomen and the lungs, there is no evidence that radiation would be of benefit, so patients with these low pathological stages but high biological risk will not be treated with abdominal radiation. Patients with Stage I or II FH tumors and either LOH 1p or LOH 16 q alone have a lesser risk for relapse than those with LOH 1p **and** 16q and an overall 4-year survival almost identical (98.1%) to those without LOH (98.4%). They will not be eligible for initial enrollment on AREN0532 and are recommended to receive standard therapy (EE-4A) and not be exposed to doxorubicin as an additional agent. Low risk Stage I and II patients will be eligible for late enrollment on AREN0532 if found to have LOH 1p and 16q.

2.1.1 Very Low Risk Favorable Histology Wilms Tumor Stratum

Current therapy for children with favorable histology Wilms tumor includes nephrectomy and stage dependent combination chemotherapy with or without radiation therapy to the abdomen and/or lungs. The available data for children who are < 2 years of age at diagnosis and who have Stage I favorable Histology Wilms tumors that weigh < 550g suggest the costs of the therapy may outweigh the benefits.¹ In NWTS-5, these patients were selected to not receive any postoperative chemotherapy or radiotherapy. Patients who relapsed, or who died of toxicity or other causes without prior relapse, were to be counted as failures.

Accrual was planned for 5 years with interim analyses after 2, 3, and 4 years of patient accrual. The stopping rule was calculated so that, if the true long-term RFS was no better than 90%, the probability of stopping early and/or concluding that “no treatment” had failed was 95%. The conservative design was based in part on the assumption that only 50% of the patients with recurrence could be successfully salvaged, as observed in patients who relapsed following initial treatment with combination chemotherapy.² In June 1998, the 3-year interim analysis showed a 2-year event free survival of 86.5%. Consequently, this part of the study was closed for further accrual, and children with recent nephrectomy were advised to receive treatment as per Regimen EE-4A.

Of the seventy-five children treated with nephrectomy only prior to closure of the protocol, 11 patients relapsed or developed metachronous disease in the contralateral kidney 0.3 – 2.3 years after diagnosis (median - 4 months, mean - 0.64 years).¹ The sites of relapse were: lung in 5 (3 bilateral, 2 unilateral) and operative bed in 3 patients. Three patients developed disease in the contralateral kidney.

Patients who developed metachronous tumors were treated based on the stage of the tumor and not as “relapsed” disease, while patients with local recurrence or new metastatic disease were treated with DD-4A therapy, which included pulmonary and/or abdominal radiotherapy based on the site of relapse. The overall survival of these eleven relapsed patients is 91%. The salvage rate in this cohort of patients from NWTS-5 is much higher (91%) than the postulated rate of 50%, a finding that supports a less conservative lower limit for the 2 year disease-free survival percentage in any future trials. Although the cohort size is limited, due to early closure of the study, these results support the hypothesis that surgery alone may be adequate treatment for this limited group of children. The current study is needed in order to confirm this hypothesis for patients with very low risk, Stage I FH Wilms tumor.

It is unknown whether chemotherapy suppresses the development of Wilms tumors within nephrogenic rests in the contralateral kidney. The NWTS5 very low risk study suggested a higher than expected incidence of tumor in the contralateral kidney but was stopped prematurely and so left this question unanswered¹. The surgery only approach of the proposed study will allow us to track whether the rate of Wilms tumor in the contralateral, remaining kidney is higher than expected. The overall risk for metachronous tumor in infants < 12 months is estimated to be approximately 4% at 6 years.³ This falls to approximately 1.5% at age 12-23 months. All of the patients in the very low risk group will be by definition < 24 months old. In addition, patients with moderate to high risk predisposition syndromes will be excluded.⁴ The acceptable rate of increase in metachronous tumors will be set at 7%; if there are

excess events beyond this number, the arm will be closed. This accepts a slightly higher relapse rate while avoiding chemotherapy in the majority of patients. We will also follow renal function in this group, to insure that the risk of severe renal compromise in patients who have metachronous relapse is not significant. It is unclear whether recurrence in the contralateral kidney will lead to a higher incidence of renal failure. This will be tracked in the follow up recommendations by rates of dialysis and the incidence of absolute GFR < 50 mL/min/1.73 m² at any time post recurrence.

LOH will not be used for assessment of exclusion of patients in the very low risk category (Stage I, tumor weight < 550 g, patient age < 2 yrs) for the following reasons: (1) Combined LOH of 1p **and** 16q has been demonstrated to be a prognostic factor in low stage disease, but LOH 1p alone was seen to be of borderline significance. NWT5 was not powered statistically for a subset analysis of Stage I very small tumors, and therefore the weight of a borderline significant result is felt to be insufficient to remove these children from eligibility for the surgery alone arm; (2) Combined LOH 1p **and** 16q occurred in only 2 of the 141 very low risk category patients on NWT5. It is expected to be a rare event in the current study; (3) These tumors are by definition completely excised and therefore biology would be anticipated to play a lesser role in outcome.

While an association between histologic features and prognosis or response to therapy has been suggested, none of these features (except anaplasia), have been statistically shown to be of significance. Of the NWT5-5 surgery-only tumors, the most important correlation between pathologic analysis and outcome was the higher frequency of recurrence or metastases in patients whose tumor was incompletely staged due to inadequate sampling of the renal sinus. This will be addressed in the current protocol by central pathology review where only patients with adequate slides for staging, as well as adequate regional lymph node sampling, will be considered eligible. The study committee recommendation for patients who are ineligible because of incomplete staging is to treat this group of children with standard treatment: EE-4A. These patients will be followed on AREN03B2 for outcome data and descriptive analysis only.

Of the tumors that recurred on the NWT5 surgery-only arm, 4 contained diffuse blastemal elements. All four of these tumors, however, had inadequate staging. Since diffuse blastemal Wilms tumor is known to demonstrate increased invasiveness and vascular involvement, it is suspected that these tumors may have been under staged, and therefore under treated. Therefore, blastemal histology alone will not be used to upstage these patients. Histology will not be used to stratify patients.

A decision analysis comparing the outcomes of these very low risk children treated with vincristine and dactinomycin (as in the NWTSG), vincristine alone (as in the United Kingdom Children's Cancer Study Group)⁵ or surgery alone (NWT5-5: arm closed early) demonstrated nearly identical projected overall survival between the vincristine alone group and the surgery alone group (98.5 vs. 98.8%). The risk benefit-ratio to each of these strategies is described below. Vincristine monotherapy has predominantly a risk associated with the insertion and presence of a central line, or if given peripherally, chemical burns. The vincristine/dactinomycin combination has additive toxicity related to veno-occlusive disease and increased risk for infection. Surgery alone has the disadvantage of potential increased therapy in the event of relapse.

Although treatment with vincristine and/or dactinomycin is considered relatively nontoxic in comparison to other regimens used in pediatric oncology, it is not without toxicity. Toxicities include complications related to the central line (thrombosis noted in up to 37% of patients when sought, infections, frequent hospital visits and antibiotics to rule out infections and the cost of care associated with a central line, morbidity associated with placement (often technically challenging in small infants), hepatotoxicity which may be fatal (and most commonly occurs in infants), neuropathy, anemia, and hair loss, as well as, the direct and indirect costs of chemotherapy and monitoring.⁶ On NWT5, there were 359 favorable

histology patients, age less than 2 years, tumor weight < 550g who had the following stage distribution: Stage I 52%, Stage II 29%, Stage III 13%, Stage IV 2%, Stage V 5%. Thus approximately half of patients will be spared a central line, and its attendant complications, as well as, any possibility of the associated toxicity of chemotherapy.

Based on these results, we plan that all Stage I patients, less than 2 years of age with a tumor weighing < 550g will be treated as **Very Low Risk** with surgery alone and observation, testing the expectation that 85% of such children will be cured through surgery alone and that over 95% of such children will ultimately survive with only the minority (< 15%) receiving chemotherapy.

Children who do suffer a recurrence are to be treated appropriately for the stage of their relapse as detailed below

- 1) **Local relapse:** These patients should be treated with Regimen DD-4A (vincristine, doxorubicin, dactinomycin) plus abdominal radiotherapy, regardless of extent of resection of the recurrence. The rationale for this approach is that there is no reason to expect that surgery alone may render the patient free of microscopic disease given the lack of confinement of the tumor to the kidney. This is not changed from the previous strategy of NWT5 V.
- 2) **Pulmonary relapse:** These patients should be treated with Regimen DD-4A (vincristine, doxorubicin, dactinomycin). All patients will complete a full 24 week course of DD-4A. All patients with pulmonary relapse will receive pulmonary radiation therapy at the beginning of chemotherapy.
- 3) **Metachronous tumors in the remaining kidney.** These patients are expected to represent approximately one third of the relapses and share in common features with bilateral Wilms tumor patients. In addition to cure, an important objective for this group of patients is renal preservation. These patients will benefit most from a surgical and chemotherapy management point of view employed for other bilateral tumor patients. Recommended management is to include excisional biopsy up front if technically feasible or biopsy and up front chemotherapy with intensified three-drug therapy (vincristine, doxorubicin, and dactinomycin) and renal parenchymal sparing surgery at 6 – 12 weeks. Surgical management of these metachronous patients is extremely complex. We recommend consultation with a renal tumors committee surgeon. The reason for this recommendation is the evidence from NWT5 IV that demonstrates an inferior event free and overall survival for children with bilateral Wilms tumor. It is believed that this inferior survival was related to inadequate up-front chemotherapy (2 drugs instead of 3 drugs) and delayed surgery. The recommended therapy will include 3 drugs and prescribed early biopsy for non-responders (6 weeks) and relatively early definitive surgery (12 weeks). No adjuvant radiation therapy is indicated if a partial nephrectomy has been performed with negative surgical margins and negative nodes/spillage.
- 4) **Other distant relapse (i.e. liver, brain).** These patients would be treated with Regimen DD-4A (vincristine, doxorubicin, dactinomycin) plus local radiotherapy, if incomplete microscopic resection. This is unchanged from previous standard therapy.

Note: It is the strong recommendation of the COG Renal Tumors Committee, if parents decline participation in the surgery and observation research protocol, that the standard therapy for very low risk patients be nephrectomy followed by Regimen EE-4A (dactinomycin and vincristine). The evidence for the safety and efficacy of a nephrectomy and observation only approach in these patients is preliminary. We suggest that it should only be undertaken in the context of a research protocol with rigorous longitudinal central radiology and pathology review.

2.1.2 Low Risk Favorable Histology Wilms Tumor Stratum

In NWTS 5, patients with Stage I favorable histology disease had a 92% RFS and 98% OS at 4 years with the Regimen EE-4A. Stage II favorable histology patients had shown 83% RFS and 92% Overall Survival at 4 years with EE-4A. The third NWTS demonstrated that Stage II patients could be effectively treated without using either doxorubicin or flank radiation.⁷ Paradoxically, in NWTS-4, these patients had a lower EFS than Stage III patients albeit with the use of doxorubicin and radiation for the latter patients.⁶ Higher risk subsets of Stage I and II patients include the 5% of patients with LOH at 1p **and** 16q who have an EFS of 74.9 and overall survival of 90%^{8,9}. Based on these results, then, we propose that the remaining Stage I and II patients without LOH 1p **and** 16q can be most effectively treated as **Low Risk** with the EE-4A chemotherapy regimen (vincristine/dactinomycin). These patients will not be initially eligible for AREN0532. Patients with local spill despite otherwise low Stage I or II disease have been shown to have a poorer EFS and have been reclassified as Stage III for this study (see Section 2.1.3).

The UKCCSG treated (1986-2001) Stage 1 patients up to 16 years of age with immediate tumor resection and 10 weekly doses of vincristine (1.5 mg/m²) alone. The 4 yr EFS/OS by age grouping was 93%/98% (< 2 yrs), 87%/95% (2-4 yrs) and 71%/87% (over 4 yrs). The COG renal tumors committee considered these data and felt that the outcomes for the UKCCSG EFS and OS were unacceptably low for patients over 2 years of age using vincristine monotherapy compared to available data from NWTS 5 (using vincristine and dactinomycin) which demonstrated the following 5 yr EFS/OS by age grouping:

Patient subset	n of patients	5-year EFS	5-year OAS
Age 0-1, surgery only	77	87%	98%
Age 0-1, EE-4A	190	94%	98%
Age 2-3, EE-4A	118	96%	97%
Age 4+, EE-4A	73	93%	98%

Note: table includes 68 patients with LOH at 1p and/or 16q, 4 patients classified as Stage IV/CT only lung disease and 2 patients with “spill”.

While it may be possible to reduce the exposure of some patients less than 2 years old with Stage I but larger tumors (> 550 g) to dactinomycin, the outcomes of this subset appear identical in NWTS and UK data. The veno-occlusive disease risk with current dosing of dactinomycin is very low at approximately 1%, therefore the COG Renal Tumors Committee felt it is appropriate to continue this standard treatment.

The SIOP 93-01 trial demonstrated that Stage 1 tumors of “intermediate-risk” and anaplastic histology could be treated with 8 doses of vincristine and 3 doses of dactinomycin with 5 yr EFS of 87% and OS of 95%, rather than the previous SIOP standard 10 vincristine and 4 dactinomycin (EFS 88% and OS 95%).^{8,10} The current SIOP 2001 trial treats these patients with the 8 week regimen - 8 doses of vincristine and 3 doses of dactinomycin. As most of the episodes of SOS (sinusoidal obstruction syndrome, formerly known as VOD) occur early in the course of therapy (with second or third dose),¹¹ it was not clear that a reduction in duration of therapy of this magnitude contributed significantly to a reduction in morbidity from dactinomycin. NWTS data suggest a superior outcome for Stage I, patient age > 2 yrs or tumor weight > 550g with an EFS 92% and OS 97% with 18 weeks therapy. Based on these results we propose that the remaining Stage I and II patients without LOH 1p **and** 16q can be most effectively treated as **Low Risk** with the EE-4A chemotherapy regimen (vincristine/dactinomycin).

The treatment and clinical outcomes will be collected on AREN03B2 and correlated with biological markers assayed on AREN03B2. If LOH 1p and 16q is identified, the patient then becomes eligible for enrollment on AREN0532 by Week 4 and treatment with Regimen DD-4A.

2.1.3 Standard Risk Favorable Histology Wilms Tumor Stratum

On NWTS-5, patients with Stage III favorable histology tumors have a 85.3% 4 year RFS and Overall Survival of 93.9% with the use of 3 drugs (vincristine, dactinomycin, and doxorubicin) + radiotherapy. Patients with Stage III/IV with LOH of 1p and 16q have a 65.9% 4 year EFS and 75.5% OS. Stage III patients without LOH 1p **and** 16q as well as, Stage I and II patients with LOH 1p **and** 16q will receive treatment with DD-4A. Stage III patients found to have LOH of 1p **and** 16q will be taken off AREN0532 protocol therapy and eligible to enroll on the higher risk protocol, AREN0533. Standard therapy remains DD-4A. Participants wishing to enroll on AREN0533 and be eligible for Regimen M therapy must do so by the end of Week 6 of DD-4A.

Stage I and II patients with LOH will not be irradiated since they have not been identified as having local factors which would predict local recurrence. There was an equal frequency of local and distant relapse in these patients. Note that all Stage I and II patients with spill (including local needle biopsy) are being reclassified as Stage III based on NWTS5 data showing inferior Relapse Free Survival for Stage II patients (4yr RFS 70% with spill versus 84% without spill). Patients will be studied to confirm improved outcomes. Gene expression profile data will also be generated on this uniformly treated group of patients through AREN03B2. Based on these results, patients with Stage III without LOH 1p **and** 16q and Stage I and II patients with LOH 1p **and** 16q will be treated as **Standard Risk** with vincristine, dactinomycin and doxorubicin +/- radiation therapy.

Overall Schema

All patients enrolled on AREN0532 will already have been enrolled on AREN03B2 and will have specimens sent for central review and LOH status. Institutions should refer to AREN03B2 for specifics of specimen submission and timing. In general, enrollment on the appropriate therapeutic protocol and stratum will await confirmation of histologic diagnosis and staging.

Diagnostic films will also be reviewed prospectively via AREN03B2 enrollment to confirm stage. Pathological diagnosis and stage will be available within three days of receipt of slides and other required materials, allowing enrollment on the correct therapeutic protocol within 14 calendar days of surgery. LOH 1p and 16q results will be available by 21calendar days post initiation of therapy.

Patients can enroll on AREN0532 based on age, tumor weight, stage, and histology if they 1) have Stage I favorable histology Wilms tumor < 550 g and are less than 2 years old OR 2) have Stage III favorable histology Wilms tumor. Patients who have Stage I favorable histology tumors > 550g or are > 2 years old or who have Stage II favorable histology tumors should begin treatment off-protocol according to standard therapy (Regimen EE-4A). Once LOH results are available, Stage I/II patients who are found to have LOH 1p **and** 16q may be enrolled on AREN0532 and will be switched to Regimen DD-4A without radiation therapy. Stage III patients found to have LOH 1p **and** 16q will be taken off AREN0532 protocol therapy and be eligible to enroll on the higher risk protocol, AREN0533.

The following table shows an overall schema for Risk group classification and treatment of favorable histology Wilms tumors (Table 6).

Table 6. Risk Group Classification for Favorable Histology Tumors

Age	Tumor Wt	Stage	LOH (both 1p and 16q)	Rapid Response#	Risk Group	Study
< 2 yrs	< 550 g	I	Any	N/A	Very Low*	AREN0532
Any	≥ 550 g	I	None	N/A	Low	AREN03B2
≥ 2 yrs	Any	I	None	N/A	Low	AREN03B2
Any	Any	II	None	N/A	Low	AREN03B2
≥ 2 yrs	Any	I	LOH	N/A	Standard	AREN0532
Any	≥ 550 g	I	LOH	N/A	Standard	AREN0532
Any	Any	II	LOH	N/A	Standard	AREN0532
Any	Any	III	None	Any	Standard	AREN0532
Any	Any	III	LOH	Any	Higher	AREN0533
Any	Any	IV	LOH	Any	Higher	AREN0533
Any	Any	IV	None	Yes	Standard#	AREN0533
Any	Any	IV	None	No	Higher	AREN0533
Any	Any	V	Any	Any	Bilateral	AREN0534

* Must have had lymph node sampling at the time of nephrectomy to be eligible for the Observation Only arm.

The standard risk group applies to the Stage IV patients who have a rapid response, as they will receive three-drug therapy (DD-4A) and no pulmonary radiotherapy (i.e. the same therapy as standard risk patients). The rapid response status will not be known until Week 6 of therapy, as it is based on their response to chemotherapy. Thus, these patients are enrolled on AREN0533, as are all the Stage IV patients.

2.2 Future Impact

The goal of AREN0532, for Very Low and Standard Risk favorable histology Wilms Tumor, is to continue to improve relapse-free and overall survival while decreasing long term toxicity by better targeting intensity of therapy to risk of recurrence. Analysis of this defined population will serve to validate results from ongoing studies of telomerase expression and function, multidrug resistance gene expression (AREN03B3), and gene expression profiling (AREN03B4). Use of the banked specimens will also facilitate new and exploratory work on completely novel factors. In the event that a robust biological or other prognostic marker is identified by NWTs review or other relevant published literature, we anticipate closure of accrual to the relevant arm of the study and application of the newly identified marker.

While the overall survival of this group of patients exceeds 90%, event free survival is lower than 80% at 4 years for some subsets. As with other relapsed tumors, salvage therapy carries with it considerable medical and psychosocial costs and potential late effects. Ultimately this study approach hopes to lead to more accurate definition of risk groups within favorable histology Wilms tumor and subsequently to greater accuracy in treatment assignment, and reduction in unnecessary relapse therapy.

2.3 Relevant Supportive Data

The management of Wilms tumor in North America has been the target of successive trials sponsored by the National Wilms Tumor Study Group since 1969. The North American treatment strategy includes upfront nephrectomy when feasible to ascertain definitive stage and histology. Subsequent therapy is based on radiological staging, surgical staging and histology. The results of the earlier trials (NWTs 1-3) demonstrated that adjuvant chemotherapy (vincristine and dactinomycin) could effectively prevent relapse in Stage I and Stage II favorable histology Wilms tumor without the need for post operative radiotherapy.^{2,12,13} These series of studies also showed that patients with Stage III and IV favorable histology Wilms tumor had a higher EFS if treated with three chemotherapy agents (vincristine, dactinomycin and doxorubicin) in addition to radiotherapy.

The most recent published data comes from the NWTS 4 in which new single dose schedules of administration of doxorubicin and dactinomycin were examined to determine if treatment efficacy could be maintained while reducing toxicity.¹⁴ Patients were divided as Low Risk or High Risk based on stage and histology. Treatment was assigned on a randomized basis, stratified for risk. Single dosing (pulse intensive) was found to result in a 2-year relapse free survival in Low Risk patients of 91.3% for Pulse Intensive therapy and 91.4% for Standard Duration therapy. Similar equivalence was found in High Risk patients in which the 2 year RFS was 87.3% for those stratified to pulse intensive and 90.0% for those stratified to standard timing.¹⁴ In addition, the NWTS 4 study had as an objective the randomized comparison of a short (6 month) versus long (15 month) course of therapy for patients with Stage II to IV favorable histology Wilms tumor. The 4-year RFS for Low risk patients was 83.7% for those treated with short (6 month) therapy and 88.2% for those treated with longer (15 month) therapy (p=0.11). The same equivalence was found for high-risk patients (89.7% 4 yr RFS for short course and 88.8% 4 yr RFS for long course therapy; p=0.87). Both strategies of providing pulse intensive therapy and of shortening duration of therapy independently resulted in substantially fewer costs related to toxicity, hospitalization and total exposure.

NWTS 4 closed in 1994 and NWTS 5 opened in 1995 and closed in 2002 after accruing over 3000 patients. The tumors examined in NWTS included favorable and anaplastic Wilms tumor, clear cell sarcoma, rhabdoid tumors and bilateral Wilms tumor. The objective relevant to this proposal from NWTS 5 included confirmation of pilot data that loss of heterozygosity of 1p **and** 16q were associated with a poorer prognosis.^{15,16} Loss of heterozygosity of 16 q occurred in 17% of patients in the pilot and approximately 11% had loss of heterozygosity of 1p. The results of NWTS 5 patients registered and followed to Aug 17, 2004 were described above.

Previous studies completed and published by COG and others show no differences in relapse or death from tumor by race and/or gender, when such parameters were analyzed.¹⁷

3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the NCI's Cancer Trials Support Unit (CTSUS) Regulatory Office and allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSUS IRB Transmittal Sheet) and the IRB approval document(s). The CTSUS IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSUS forms can be located on the CTSUS web page (<https://www.ctsu.org>). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSUS Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206),
Emailed (CTSUSRegulatory@ctsu.cocog.org) or mailed to the CTSUS Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSUS Regulatory Helpdesk at: 1-866-651-CTSUS. For general (non-regulatory) questions, call the CTSUS General Helpdesk at: 1-888-823-5923.

3.1.2 Patient Registration

Prior to enrollment on AREN0532, patients must be assigned a COG patient ID number and enrolled on AREN03B2. This number is obtained via the eRDE system once authorization for the release of protected

health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

3.1.3 Study Enrollment

Patients may be enrolled on AREN0532 once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the eRDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG website.

3.1.4 Timing

3.1.4.1 Enrollment on AREN03B2 and Initial Risk Assignment

Enrollment on the AREN03B2 Renal Tumor Biology, Classification, and Banking Study is required **prior to** enrollment on AREN0532. Investigators are strongly encouraged to review the radiological, surgical and pathological specimen criteria for enrollment on AREN03B2 prior to nephrectomy, as an inadequate approach will not allow enrollment on AREN03B2, and thus AREN0532. Adequate lymph node sampling must occur for very low risk patients. It is strongly recommended for all other patients.

Patients will be assigned through AREN03B2 to a stratum based on an “initial risk” classification determined by clinical, radiological, surgical and pathological characteristics. Treatment will be initiated based on this “initial risk” classification.

3.1.4.2 Timing of Enrollment and Starting Protocol Therapy

Consent for study enrollment must be obtained before any AREN0532 protocol therapy is given.

All low and standard risk patients must begin chemotherapy within 14 days of nephrectomy or renal biopsy (surgery/biopsy is Day 0), unless medically contraindicated. Physicians are encouraged not to begin treatment until the central radiology, surgery, and pathology reviews are completed and an initial risk assignment is made on the AREN03B2 study. However, treatment may begin before central review on AREN03B2 is completed if medically indicated (e.g., significant symptoms from large tumor burden).

Initial Standard Risk

Patients initially assigned as standard risk patients may enroll on AREN0532 and start therapy before obtaining the LOH results. Study enrollment must take place within seven (7) calendar days after beginning protocol therapy for patients with initial standard risk disease unless condition (a) or (b) stipulated below occurs. Seven calendar days do not include the start date.

If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than **seven** (7) calendar days after enrollment or **by Day 14** following surgery, whichever occurs first. If all the required specimens and materials were submitted for central review by Day 7 but initial risk assignment has not occurred by Day 12 or within 5 days of starting treatment (whichever occurs first), please notify the AREN03B2 Study Chair and Research Coordinator to discuss the status of the risk assignment.

If patient reaches Day 14 (post surgery) or Day 7 (of starting treatment) without initial risk assignment, patient will not be eligible for enrollment unless: (a) central pathology required further diagnostic tests, or (b) materials and specimens arrived by Day 7 and central review did not occur by Day 14. In these circumstances, the patient may proceed with treatment according to local institutional risk assessment (after obtaining appropriate protocol consent) and enroll within 3 working days of notification of central initial risk assignment, if the central risk assignment is in agreement with the local institution's assessment.

Initial Low Risk

Patients initially assigned as low risk patients may **not** enroll on AREN0532 before obtaining the LOH results. Final risk assignment – and thus, eligibility for AREN0532 – for this arm may potentially be affected by the results of the LOH testing. These results are expected to be obtained within 3 weeks of tumor submission. Patients with initial risk assignment of Low Risk disease will be followed on AREN03B2. Standard treatment is Regimen EE-4A, which must be started by Day 14 following nephrectomy (unless medically contraindicated) for the patient to be eligible for AREN0532. Low risk patients found to have LOH 1p and 16q (and who have had treatment with EE-4A) will receive a final risk assignment indicating upgrading to Standard Risk and eligibility for AREN0532 Stratum 5.

Study enrollment must take place within seven (7) calendar days after beginning AREN0532 protocol-prescribed DD-4A therapy on Stratum 5 unless condition (a) or (b) stipulated below occurs. Seven calendar days do not include the start date. These patients must enter by Week 4 of the DD-4A regimen. If all the required specimens and materials were submitted for central review by Day 7 but initial risk assignment has not occurred within 5 days of starting treatment, please notify the AREN03B2 Study Chair and Research Coordinator to discuss the status of the risk assignment.

If patient reaches Day 7 of starting treatment without initial risk assignment, patient will not be eligible for enrollment unless: (a) central pathology required further diagnostic tests, or (b) materials and specimens arrived by Day 7 and central review did not occur by Day 14. In these circumstances, the patient initially assigned as low risk may proceed with treatment according to local institutional risk assessment (after obtaining appropriate protocol AREN03B2 consent). Subsequent enrollment on AREN0532 Stratum 5 may only occur after the final risk assignment has been provided.

Very Low Risk

Patients initially assigned as very low risk patients may enroll on AREN0532 before obtaining the LOH results. The LOH results will not impact the assigned stratum for very low risk patients. Patients who are eligible for the very low risk arm (Stage I, tumor weight < 550 g, age < 2 years) may enroll up to 30 days following nephrectomy. **To be eligible for this stratum, the patient must have undergone lymph node biopsy.** If all the required specimens and materials were submitted for central review by Day 7 but initial risk assignment has not occurred by Day 12, please notify the AREN03B2 Study Chair and Research Coordinator to discuss the status of the risk assignment.

If patient reaches Day 14 without initial risk assignment, patient will not be eligible for enrollment unless: (a) central pathology required further diagnostic tests, or (b) materials and specimens arrived by Day 7 and central review did not occur by Day 14. In these circumstances, the patient may enroll once the central review is available up to 30 days following nephrectomy, if the central risk assignment is in agreement with the local institution's assessment.

For both initial standard and initial low risk patients, if enrollment takes place before starting therapy, the date protocol therapy is projected to start is open since there are unforeseen medical complications that may delay a patient's actual start of protocol therapy. However, if the start of protocol therapy is more

than seven days after enrollment, the medical indication for the delay must be documented in the patient's medical/research record.

3.1.4.3 Timing of Radiation Therapy Scheduling

Patients with a renal mass should be scheduled for simulation and radiation therapy at diagnosis. Radiation therapy can then be canceled if not required by "initial risk" assignment provided by central review on AREN03B2.

3.1.5 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.2 **Patient Criteria**

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.

3.2.1 Age

Patients must be less than 30 years of age at the time of diagnosis.

3.2.2 Diagnosis

Patients must have previously enrolled on AREN03B2 and be found to have newly diagnosed Stage I-III favorable histology Wilms tumor, confirmed by central pathology, surgical and radiology review.

Note: Patients will be assigned through AREN03B2 to a stratum based on an "initial risk" classification determined by clinical, radiological, surgical and pathological characteristics. Stage I favorable histology patients with tumor ≥ 550 g or ≥ 2 years of age, and Stage II favorable histology patients may not enroll on AREN0532 before obtaining a final risk classification indicating that the patient is eligible for Stratum 5 based on the results of the LOH testing. Patients assigned as very low or standard risk favorable histology should enroll on AREN0532 and start treatment before obtaining the LOH results. Treatment for very low risk patients will not be modified based on LOH results. For patients with very low risk tumors (Stage I favorable histology < 550 g and age < 2 years), lymph node sampling must occur. Treatment will be initiated based on this "initial risk" classification. By three weeks, a "final risk" classification will be assigned based on LOH findings and this "final risk" stratification will be used for assigning continuing treatment. Investigators will be notified of this final stratification.

- a) Patients will be eligible for the very low risk arm (surgery and observation only) if they have Stage I, Favorable Histology Wilms tumor, are < 2 yrs of age, and have a tumor weight < 550 g. They also must have had adequate submission of regional lymph nodes demonstrating histologically nodes negative for tumor and confirmation of absence of pulmonary metastases on CT scan of chest by central radiology review.
- b) Patients will be eligible for the standard risk arm (DD-4A) with no radiotherapy, if they have Loss of Heterozygosity for 1p **and** 16q, AND are either Stage I, Favorable Histology, Wilms tumor (age ≥ 2 years or tumor weight of ≥ 550 g), **or** Stage II, Favorable Histology, Wilms tumor with of any weight of tumor or patient age.
- c) Patients will be eligible for the standard risk arm (DD-4A) with radiotherapy, if they have no Loss of Heterozygosity for 1p **and** 16q and have Stage III, Favorable Histology Wilms tumor. Note: Patients found to have combined LOH at 1p **and** 16q will be taken off AREN0532 protocol therapy and eligible to enroll on AREN0533.

Patients with synchronous bilateral Wilms tumors (Stage V) and some patients predisposed to develop bilateral Wilms tumors are **not** eligible for the very low risk observation arm of AREN0532 and should be directed to AREN0534. **Predisposition syndromes excluded from the observation arm of AREN0532 include unilateral Wilms tumor and any of the following: aniridia, Beckwith-Wiedemann syndrome, isolated hemihypertrophy, Simpson-Golabi-Behmel syndrome, Denys-Drash syndrome or other associated genito-urinary anomalies, multicentric Wilms tumor, unilateral WT with contralateral nephrogenic rest(s) in a child under two years of age, and diffuse hyperplastic perilobar nephroblastomatosis. Also excluded are:** patients with Familial Wilms Tumor defined as Wilms tumor in a patient with a known constitutional Familial Wilms tumor gene mutation, and/or Wilms tumor in a patient who has at least one first or second degree relative with Wilms tumor (sibling, parent, aunt/uncle, grandparent, first cousin). **All other lower risk predisposition syndromes are allowed.**

3.2.3 Specimen Submission

Specimens/materials per Section 5.1 of AREN03B2 (available at: <https://members.childroncologygroup.org/Prot/AREN03B2/AREN03B2Subrequire&recomm.pdf>) must be submitted for central review **by Day 7 at the latest.**

Timing considerations:

- Patients must begin protocol therapy on AREN0532 by Day 14 after surgery or biopsy, unless medically contraindicated.

3.2.4 Performance Level (See Appendix I)

The Karnofsky performance status must be ≥ 50 for patients >16 years of age and the Lansky performance status must be ≥ 50 for patients ≤ 16 years of age.

3.2.5 Prior Therapy

No prior tumor-directed chemotherapy or radiotherapy is acceptable, except if previously treated with EE-4A and enrolling from AREN03B2 with Stage I or II Favorable Histology Wilms tumor found to have LOH 1p and 16q, or for those treated for emergent issues, as medically indicated.

3.2.6 Organ Function Requirements:

3.2.6.1 Adequate liver function defined as:

- Total (direct) bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) and SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age.

3.2.6.2 For patients assigned to Standard risk stratum (DD-4A): Adequate cardiac function defined as:

- Shortening fraction of $\geq 27\%$ by echocardiogram, or
- Ejection fraction of $\geq 50\%$ by radionuclide angiogram.

3.2.7 Other

Female patients of childbearing potential must have a negative pregnancy test.

3.2.7.1

Female patients who are lactating must agree to stop breastfeeding.

3.2.7.2

Sexually active patients of childbearing potential must agree to use effective contraception.

3.2.8 Regulatory

3.2.8.1

All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.8.2

All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

Three treatment Regimens will be applied according to tumor histology, stage, and response to treatment.

Age	Tumor Wt	Stage	LOH (both 1p and 16q)	Rapid Response #	Risk Group	Therapy
< 2 yrs	< 550 g	I	Any	N/A	Very Low	Surgery only
Any	≥ 550 g	I	None	N/A	Low	EE-4A**
≥ 2 yrs	Any	I	None	N/A	Low	EE-4A**
Any	Any	II	None	N/A	Low	EE-4A**
≥ 2 yrs	Any	I	LOH	N/A	Standard	DD-4A
Any	≥ 550 g	I	LOH	N/A	Standard	DD-4A
Any	Any	II	LOH	N/A	Standard	DD-4A
Any	Any	III	None	Any	Standard	DD-4A*

* Radiation therapy begins at Week 1 except if delayed resection.

** Recommended (patients will not be treated on the AREN0532 study unless found to have LOH).

Most patients will have had surgical resection before beginning chemotherapy, as outlined in AREN03B2. Patients with initially unresectable or incompletely resected tumors will receive chemotherapy and undergo imaging reevaluation after 2 cycles (approximately 6 weeks). If the tumor is deemed resectable at Week 6, further surgery will be performed. Surgical principles should be followed as outlined in Section 13.

Protocol therapy (chemotherapy and radiation therapy) should begin as soon as possible after surgery **once all centrally reviewed data is available and initial risk assignment is received from AREN03B2. Timely submission of required data to AREN03B2 is essential.** Protocol therapy must begin by Day 14 after the original surgery or biopsy (surgery/biopsy is Day 0), unless medically contraindicated. If the specimens were submitted for central review by Day 7 and there is no return of central pathology review by Day 14, the patient may proceed with treatment according to local risk assessment and enroll once the central review is available.

GENERAL CHEMOTHERAPY GUIDELINES

1. No dose of dactinomycin or DOXOrubicin should be initiated if the absolute neutrophil count is < 750/ μ L or the platelet count is < 75,000/ μ L

2. Babies < 12 months of age should receive ONE-HALF of the recommended doses of vinCRISTine and dactinomycin as calculated on the basis of body weight. Full doses of chemotherapeutic agents should be administered to these patients when they reach \geq 12 months of age during treatment on study. Dosing for babies < 12 months of age will be calculated per kilogram of weight.
3. Dactinomycin and DOXOrubicin should be reduced by 50% if it is given during, or within 6 weeks after completion of administration of whole lung or whole abdominal XRT only.
4. **Special precautions regarding vinCRISTine: FOR INTRAVENOUS USE ONLY.**
The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."
5. The World Health Organization, the Institute of Safe Medicine Practices (United States), and the Safety and Quality Council (Australia) all support the use of minibag rather than syringe for the infusion of vinCRISTine. For pharmacokinetic purposes on this study, the delivery of vinCRISTine via either IV slow push or minibag is acceptable.
6. Concomitant medications restrictions:
Clinically significant drug interactions have been reported when using vinCRISTine with strong CYP450 3A4 inhibitors and inducers. Selected strong inhibitors or stimulators of cytochrome P450 3A4, include azole antifungals (such as fluconazole, voriconazole, itraconazole, ketoconazole) rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's wort. These drugs should be avoided with vinCRISTine.

The clinical outcome and significance of CYP450 interactions with DOXOrubicin, is less clear. CYP450 3A4 stimulators or inhibitors should be avoided or used with great caution. Aprepitant also interacts with CYP3A4 and should be used with caution with vinCRISTine chemotherapy.

Additional inducers or inhibitors of CYP450 enzymes can be found at <http://medicine.iupui.edu/clinpharm/ddis/>.

Very low risk FH Wilms tumor (Age < 2 years, Tumor weight < 550 g, Stage I) receive surgery alone and close observation.

These patients will have had a nephrectomy alone. If they meet the classification criteria for very low risk, these patients will receive no further therapy unless relapse is documented. Follow up recommendations are to be strictly followed and are outlined in Section 7.2.1.

Details of management of patients with recurrent tumor following surgery alone and observation are provided in Section 13.6. Briefly, all patients who develop recurrent tumor, whether locally in the abdomen or as distant metastases, (but not metachronous relapse) will undergo immediate surgery if resection is thought possible. Otherwise, they will undergo biopsy then delayed resection following 6 weeks of chemotherapy. All patients (not metachronous relapse) will receive Regimen DD-4A as detailed in Section 4.3 below. Three drug therapy is indicated in patients with local relapse, as the tumor is no longer confined within a renal capsule, indicating higher stage of disease. All local recurrences will receive upfront radiotherapy.

If the tumor occurs in the contralateral kidney, excisional biopsy should occur if the lesion is small. Otherwise, the patient should receive pre resection chemotherapy to facilitate partial nephrectomy – using Regimen DD-4A for all patients to maximize the chance of partial nephrectomy. The aim of this strategy is to provide renal parenchymal sparing surgery to the remaining kidney.

4.2 Treatment Plan: Regimen DD-4A

Regimen DD-4A combines the following therapeutic agents: vinCRISTine (VCR1 and VCR2), dactinomycin (DACT), and DOXOrubicin (DOXO1 and DOXO4), as well as radiation therapy (XRT).

This regimen will be administered in 2 courses:

- Course 1: Weeks 1-12 (84 days), composed of 4 cycles,
- Course 2: Weeks 13-28 (112 days), composed of 5 cycles.

The use of myeloid growth factors is not recommended for this regimen.

Patients who will receive Regimen DD-4A

- Stage I-II favorable histology Wilms tumor with combined LOH 1p and 16q: Entry to Regimen DD-4A at Week 4 (these patients will **not** receive XRT).
- Stage III favorable histology Wilms tumor without combined 1p and 16q: Entry to Regimen DD-4A at Week 1 (these patients will receive XRT; see the radiation therapy guidelines on the next page).
- Stage I very low risk patients with relapse after observation only (most of these patients will receive XRT; see the radiation therapy guidelines on the next page).

Criteria to start Regimen DD-4A

Begin Regimen DD-4A when ANC \geq 750/ μ L and platelet count \geq 75,000/ μ L.

See protocol Section 5.0 for dose modifications for toxicities.

Required observations

See protocol Section 7.0 for a complete list of observations.

Cycle 1			Cycle 2			Cycle 3			Cycle 4			Reporting Period 1 ends at Week 12 Evaluation (4 cycles)	
Wk 1	2	3	Wk 4	5	6 ¹	Wk 7	8	9	Wk 10	11	12 ¹		
DACT ²						DACT ²							
			DOXO ⁴						DOXO ⁴				
VCR1	VCR1	VCR1	VCR1	VCR1	VCR1	VCR1	VCR1	VCR1	VCR1				
XRT ²						XRT ²							
Cycle 5			Cycle 6			Cycle 7			Cycle 8			Cycle 9	Reporting Period 2 ends at Week 28 Evaluation (5 cycles)
Wk 13 ²	14	15	Wk 16	17	18	Wk 19	20	21	Wk 22	23	24	Wk 25	
DACT ²						DACT ²						DACT ²	
			DOXO ¹						DOXO ¹				
VCR2			VCR2			VCR2			VCR2			VCR2	
XRT ²													

¹ Perform surgical resection if the primary tumor was not resected at the time of diagnosis and the Week 6 or 12 imaging studies indicate that resection is feasible.

² Refer to the radiation therapy section on the next page.

³ Dose reduction guidelines with XRT: Refer to the radiation therapy section on the next page.

VCR1	VinCRISTine	0.025 mg/kg/dose IV x 1 for infants < 1 yr 0.05 mg/kg/dose IV x 1 for children 1 yr to 2.99 yrs 1.5 mg/m ² /dose IV x 1 for children \geq 3 yrs.	Maximum dose: 2 mg
VCR2	VinCRISTine	0.034 mg/kg/dose IV x 1 for infants < 1 yr 0.067 mg/kg/dose IV x 1 for children 1 yr to 2.99 yrs 2 mg/m ² /dose IV x 1 for children \geq 3 yrs.	Maximum dose: 2 mg
DACT ² *	Dactinomycin	0.023 mg/kg/dose IV x 1 for infants < 1 yr 0.045 mg/kg/dose IV x 1 for children \geq 1 yr	Maximum dose: 2.3 mg
DOXO ⁴ *	DOXOrubicin	1.5 mg/kg/dose IV x 1 for infants < 1 yr 45 mg/m ² /dose IV x 1 for children \geq 1 yr	
DOXO1	DOXOrubicin	1 mg/kg/dose IV x 1 for infants < 1 yr 30 mg/m ² /dose IV x 1 for children \geq 1 yr	

* The dosages DACT1, DOXO2, and DOXO3 are not used on this protocol.

Therapy

• **Radiation therapy**

Radiation therapy (XRT) will begin at Week 1 for patients whose primary tumors were resected initially. For patients with delayed tumor resection, radiation therapy should begin after the primary tumor is resected, usually at Week 7 or 13.

The doses of DOXOrubicin and dactinomycin should be reduced by 50% if DOXOrubicin or dactinomycin is given during or within 6 weeks of completing a course of whole abdomen or lung XRT (but not after flank irradiation). The full DOXOrubicin or dactinomycin dose may be given if it coincides with the start of XRT.

Notes: - **No radiation therapy should be given to patients with Stage I-II favorable histology Wilms tumor with combined LOH 1p and 16q.**

- Stage III FH WT patients will receive radiation therapy as detailed in Section 16.0.

- Stage I very low risk relapsed patients will receive radiation therapy as detailed in Section 16.0.

See protocol Section 16.0 for radiation therapy guidelines.

• **Chemotherapy**

Notes: - VinCRiStine should be held until peristalsis is reestablished after surgery.

- First dose of chemotherapy is considered Day 1 of Week 1.

- It is strongly recommended that chemotherapy begin by Day 9 after the histologic diagnosis is made (surgery/biopsy being Day 0), but may not begin later than Day 14, unless medically contraindicated.

Course 1 (Weeks 1 to 12):

Dactinomycin (DACT2): IV push over 1-5 minutes on Day 1 of Weeks 1 and 7 (Maximum dose: 2.3 mg)

0.023 mg/kg/dose for infants < 1 yr

0.045 mg/kg/dose for children \geq 1 yr

Dosage guidelines with XRT: If administered during or within 6 weeks of completing a course of whole lung or whole abdomen XRT, the dactinomycin dose should be reduced by 50%. The full dactinomycin dose may be given if it coincides with the start of XRT.

VinCRiStine (VCR1): IV push over 1 minute (or infusion via minibag as per institutional policy) on Day 1 of Weeks 1-10 (Maximum dose: 2 mg)

0.025 mg/kg/dose for infants < 1 yr

0.05 mg/kg/dose for children 1 yr to 2.99 yrs

1.5 mg/m²/dose for children \geq 3 yrs

Medication errors have occurred due to confusion between vinBLASStine and vinCRiStine.

Special precautions regarding vinCRiStine: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRiStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

DOXOrubicin (DOXO4): IV over 15-120 minutes on Day 1 of Weeks 4 and 10

1.5 mg/kg/dose for infants < 1 yr

45 mg/m²/dose for children \geq 1 yr

Dosage guidelines with XRT: If administered during or within 6 weeks of completing a course of whole lung or whole abdomen XRT, the DOXOrubicin dose should be reduced by 50%. The full DOXOrubicin dose may be given if it coincides with the start of XRT.

Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable.

Course 2 (Weeks 13 to 28):

Dactinomycin (DACT2): IV push over 1-5 minutes on Day 1 of Weeks 13, 19, and 25

(Maximum dose: 2.3 mg)

0.023 mg/kg/dose for infants < 1 yr

0.045 mg/kg/dose for children \geq 1 yr

Dosage guidelines with XRT: If administered during or within 6 weeks of completing a course of whole lung or whole abdomen XRT, the dactinomycin dose should be reduced by 50%. The full dactinomycin dose may be given if it coincides with the start of XRT.

VinCRISTine (VCR2): IV push over 1 minute (or infusion via minibag as per institutional policy) on Day 1 of Weeks 13, 16, 19, 22, and 25 (Maximum dose: 2 mg)

0.034 mg/kg/dose for infants < 1 yr

0.067 mg/kg/dose for children 1 yr to 2.99 yrs

2 mg/m²/dose for children \geq 3 yrs

Medication errors have occurred due to confusion between vinBLASTine and vinCRISTine.

Special precautions regarding vinCRISTine: FOR INTRAVENOUS USE ONLY.

The container or the syringe containing vinCRISTine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

DOXOrubicin (DOXO1): IV over 15-120 minutes on Day 1 of Weeks 16 and 22

1 mg/kg/dose for infants < 1 yr

30 mg/m²/dose for children \geq 1 yr

Dosage guidelines with XRT: If administered during or within 6 weeks of completing a course of whole lung or whole abdomen XRT, the DOXOrubicin dose should be reduced by 50%. The full DOXOrubicin dose may be given if it coincides with the start of XRT.

Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. The conventional and liposomal formulations are NOT interchangeable.

Therapy Delivery Maps

The Therapy Delivery Maps (TDMs) for Regimen DD-4A are on the next 2 pages.

Following completion of Regimen DD-4A:

End of therapy after Week 25 chemotherapy. End of reporting period at Week 28 evaluation.

4.2.1 <u>AREN0532: Administration Schedule for Regimen DD-4A, Weeks 1-12</u> Regimen DD-4A combines chemotherapy and radiation therapy. Myeloid growth factors are not recommended for this regimen.	_____	_____
	Patient name or initials	DOB

Criteria to start cycle: ANC ≥ 750/μL and platelet count ≥ 75,000/μL. This course lasts 84 days (12 weeks). The Therapy Delivery Map for this course is 1 page long.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dactinomycin± (DACT2)	IV push over 1-5 minutes	0.023 mg/kg/dose for infants < 1 yr 0.045 mg/kg/dose for children ≥ 1 yr	1 (Wks 1 & 7)	Maximum dose: 2.3 mg	a. History b. Physical exam (Ht, Wt, BSA, VS), electrolytes c. CBC (diff/plt), creat., SGOT, SGPT, bili. (obtain <u>weekly</u> until Wk 10) d. Total protein/albumin e. Urinalysis f. CT chest (at Wk 7: required only for patients with pulmonary relapse from the VLR arm [observation only]) g. CT or MRI abdomen/pelvis (at Week 7: only for patients with measurable residual disease after initial surgery – evaluate for delayed resection in Stage III patients) h. Chest X-ray i. Abdominal ultrasound (recommended if IVC tumor thrombus cannot be excluded on CT) j. Performance status k. Echo and ECG OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE.
± If administered during or within 6 weeks of completing a course of whole lung or whole abdomen XRT, the dactinomycin and DOXOrubicin doses should be reduced by 50%. The full dactinomycin or DOXOrubicin dose may be given if it coincides with the start of XRT.					
VinCRISTine (VCR1)	IV push over 1 minute^^	0.025 mg/kg/dose for infants < 1 yr 0.05 mg/kg/dose for children 1 yr to 2.99 yrs 1.5 mg/m ² /dose for children ≥ 3 yrs	1 (Wks 1-10)	Maximum dose: 2 mg ^^ (or infusion via minibag as per institutional policy)	
DOXOrubicin± (DOXO4)	IV over 15- 120 minutes	1.5 mg/kg/dose for infants < 1 yr 45 mg/m ² /dose for children ≥ 1 yr	1 (Wks 4 & 10)		

Week 1: Ht _____ cm Wt _____ kg BSA _____ m² Week 4: Ht _____ cm Wt _____ kg BSA _____ m²
Week 7: Ht _____ cm Wt _____ kg BSA _____ m² Week 10: Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Cycle	Week	Day	DACT2 Calc. dose: _____mg	VCR1 Calc. dose: _____mg	DOXO4 Calc. dose: _____mg	Studies	Comments (Include any held dose or dose modification)	
Enter calculated dose above and actual dose administered below.										
		1	1	1	_____mg	_____mg		a - k		
			2	1	_____mg	_____mg		c		
			3	1	_____mg	_____mg		c		
		2	4	1	_____mg	_____mg	_____mg±	b, c		
			5	1	_____mg	_____mg		c		
			6	1	_____mg	_____mg		c		
		3	7	1	_____mg±	_____mg		a - c, e - g		
			8	1	_____mg	_____mg		c		
			9	1	_____mg	_____mg		c		
		4	10	1	_____mg	_____mg	_____mg±	b, c		
			11		No chemotherapy.					
			12		No chemotherapy. Evaluation before start of Week 13 chemo.					
			13		Continue to Cycle 5. (Perform surgery if the primary tumor was not resected at the time of diagnosis and the Week 13 imaging studies indicate that resection is feasible.)					

SEE PROTOCOL APPENDIX II FOR SUPPORTIVE CARE GUIDELINES, SECTION 5.0 FOR DOSE MODIFICATIONS, AND SECTION 16.0 FOR RADIATION THERAPY GUIDELINES.

4.2.2 AREN0532: Administration Schedule for Regimen DD-4A, Weeks 13-28
Regimen DD-4A combines chemotherapy and radiotherapy.
Reminder: Myeloid growth factors are not recommended for this regimen.

Patient name or initials

DOB

Criteria to start cycle: ANC \geq 750/ μ L and platelet count \geq 75,000/ μ L. This course lasts 112 days (16 weeks). The Therapy Delivery Map for this course is 1 page long.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
Dactinomycin \pm (DACT2)	IV push over 1-5 minutes	0.023 mg/kg/dose for infants < 1 yr 0.045 mg/kg/dose for children \geq 1 yr	1 (Wks 13, 19 & 25)	Maximum dose: 2.3 mg	a. History b. Physical exam (Ht, Wt, BSA, VS), electrolytes c. CBC (diff/plt), creat., SGOT, SGPT, bili. (obtain before each cycle [from Wk 13]) e. Urinalysis f. CT chest (required only for patients with pulmonary relapse from the Very Low Risk arm [observation only]) g. CT or MRI abdomen/pelvis (at Wk 13: only if unresectable Stage III disease was identified at diagnosis or at Week 6. This scan is to be used for assessment for surgery.) h. Chest X-ray i. Abd. ultrasound (not needed at Wk 13 if CT/MRI is used) j. Performance status k. Echo
\pm If administered during or within 6 weeks of completing a course of whole lung or whole abdomen XRT, the dactinomycin and DOXOrubicin doses should be reduced by 50%. The full dactinomycin or DOXOrubicin dose may be given if it coincides with the start of XRT.					
VinCRISTine (VCR2)	IV push over 1 minute ^{^^}	0.034 mg/kg/dose for infants < 1 yr 0.067 mg/kg/dose for children 1 yr to 2.99 yrs 2 mg/m ² /dose for children \geq 3 yrs	1 (Wks 13, 16, 19, 22 & 25)	Maximum dose: 2 mg ^{^^} (or infusion via minibag as per institutional policy)	
DOXOrubicin \pm (DOXO1)	IV over 15- 120 minutes	1 mg/kg/dose for infants < 1 yr 30 mg/m ² /dose for children \geq 1 yr	1 (Wks 16 & 22)		OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE.

Week 13: Ht _____ cm Wt _____ kg BSA _____ m² Week 16: Ht _____ cm Wt _____ kg BSA _____ m²
Week 19: Ht _____ cm Wt _____ kg BSA _____ m² Week 22: Ht _____ cm Wt _____ kg BSA _____ m² Week 25: Ht _____ cm Wt _____ kg BSA _____ m²

Date Due	Date Given	Cycle	Week	Day	DACT2 Calc. dose: _____ mg	VCR2 Calc. dose: _____ mg	DOXO1 Calc. dose: _____ mg	Studies	Comments (Include any held dose or dose modification)
Enter calculated dose above and actual dose administered below.									
		5	13	1	_____ mg \pm	_____ mg		b, c, e, g, h, i	
			14		No chemotherapy.				
			15		No chemotherapy.				
		6	16	1	_____ mg	_____ mg	_____ mg \pm	b, c, k	
			17		No chemotherapy.				
			18		No chemotherapy.				
		7	19	1	_____ mg \pm	_____ mg		b, c, f	
			20		No chemotherapy.				
			21		No chemotherapy.				
		8	22	1	_____ mg	_____ mg	_____ mg \pm	b, c, h, i	
			23		No chemotherapy.				
			24		No chemotherapy.				
		9	25	1	_____ mg	_____ mg		b, c	End of therapy after Week 25 chemotherapy.
			26		No chemotherapy.				
			27		No chemotherapy.				
			28		End of reporting period at Week 28 evaluation.			a - c, e, f, g, j, k	

SEE PROTOCOL APPENDIX II FOR SUPPORTIVE CARE GUIDELINES, SECTION 5.0 FOR DOSE MODIFICATIONS, AND SECTION 16.0 FOR RADIATION THERAPY GUIDELINES.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

For questions related to dose modifications or unexpected toxicity, notify the disease-specific study coordinators listed in the introduction.

ALL MODIFICATIONS OF THERAPY SHOULD BE EXPLAINED AND DOCUMENTED.

5.1 Hematological Toxicity

5.1.1 Hematological Parameters

The initiation of myelosuppressive courses of chemotherapy should be delayed until the ANC is $\geq 750/\mu\text{L}$ and the platelet count is $\geq 75,000/\mu\text{L}$. VinCRISTine, when given alone in the weekly schedules, should be continued without regard to ANC or platelet count. If DOXOrubicin or dactinomycin is held during the every-three-week portion of the schedule, vinCRISTine should be delayed until the DOXOrubicin or dactinomycin is resumed.

5.1.2

Dosages of myelosuppressive agents should be reduced if that particular chemotherapy combination results in a delay of the subsequent chemotherapy course by more than one week (8 days or more). For example, if a delay occurs after a course of vinCRISTine/DOXOrubicin, the dosages of doxorubicin should be reduced by 25% in the next vinCRISTine/DOXOrubicin course. If the dose reduction of 25% continues to result in treatment delays, the dosages should be reduced to 50% of the original dosages.

5.1.3

If the patient tolerates the reduced dose therapy without delay of the subsequent chemotherapy course by more than one week, escalate back up to full dose. If delays reoccur, the doses should again be reduced by 25%.

5.1.4

It is important not to have interruptions in radiation therapy unless the patient is clinically ill. Radiation should be interrupted for an ANC $< 300/\mu\text{L}$ (or platelets $< 40,000/\mu\text{L}$) and may be resumed when the counts recover (see Section 16.3). If XRT is interrupted, this should be documented.

5.2 Infection and Fever

5.2.1

Dosages of myelosuppressive agents should be reduced if that particular chemotherapy combination results in a life-threatening infection (Grade 4) or a complicated episode of febrile neutropenia. A complicated febrile neutropenia episode includes hypotension requiring more than one fluid bolus or any pressor, admission to an intensive care setting because of clinical concern, typhlitis, meningitis, or lung infection for which mechanical ventilation is needed. These criteria apply even if there is no documented positive blood culture. However, uncomplicated bacteremia is not an indication to reduce doses of chemotherapy.

5.2.2

Dosages of myelosuppressive agents should be reduced by 25% according to the guidelines outlined in Section 5.1.2. If reduced dosages are well tolerated, an attempt should be made to escalate the dosages to their original levels.

5.3 Mucositis

Mucositis that interferes with oral fluid intake necessitating IV fluids or NG fluids should result in a 25% decrease in the doses of dactinomycin, or DOXOrubicin, with the next dose. The dosage may be escalated back to 100% if subsequent doses are not associated with significant mucositis.

5.4 Radiation Dermatitis and Radiation Recall Risk

If a patient has wet dermatitis (moist skin desquamation) after radiation therapy, dactinomycin and DOXOrubicin doses should be omitted and made up later when this clears. If a patient has erythema or dry desquamation, the doses of dactinomycin or DOXOrubicin should be decreased by 50%. Children who receive full-abdominal radiation therapy or whole lung radiation should have the doses of dactinomycin or DOXOrubicin reduced to 50% if to be given during the course of XRT or within 6 weeks of the completion of radiation (unless DOXOrubicin or dactinomycin are given concurrent with the start of XRT).

5.5 Gastrointestinal Toxicity (Diarrhea and Typhlitis)

Severe treatment-related diarrhea is an indication to interrupt temporarily a course of abdominal radiation therapy if underway, or to delay a scheduled dose of dactinomycin or DOXOrubicin. If severe diarrhea occurs as a complication after two successive courses, infectious causes for this diarrhea (including potentially *C.difficile*) should be sought and, if not present, subsequent courses of the associated chemotherapy agent reduced by 25%. Dose may be escalated if diarrhea subsides.

If typhlitis occurs during or after a course of chemotherapy, further chemotherapy should be held until the typhlitis resolves. Subsequent courses of the associated chemotherapy agent should be reduced by 25%.

5.6 Vincristine-Related Toxicity (neuropathy/constipation)

VinCRISStine should be held until peristalsis is reestablished after surgery. Appropriate interventions to prevent or control constipation should be instituted. It is expected that patients on weekly vinCRISStine will have depressed or absent deep tendon reflexes or moderate weakness and this is not a reason to modify therapy. Jaw pain or paresthesias that are not controllable with pain medications, paralytic ileus, peripheral neuropathies that significantly impair activities of daily living, and cranial nerve palsies (including ptosis, diplopia, and vocal cord paralysis) are indications for omission of one or two doses of vinCRISStine. Once the neuropathies resolve, the drug should be restarted at 50% of the previous dose, and increased in increments of 25% to full dose, if subsequent doses are not associated with recurrence of signs of severe neuropathy. Other scheduled chemotherapy should be given as scheduled, if there are no specific contraindications.

5.7 Cardiac Abnormalities

Asymptomatic premature beats, ST-T wave abnormalities, prolongation of the electrocardiogram QT corrected interval (> 0.44 sec corrected), cardiac disorders not previously present, and reduction of myocardial function (ejection fraction $< 50\%$ or shortening fraction $< 28\%$) are indications for delaying DOXOrubicin-containing chemotherapy courses for one week. After a week, the cardiac studies should be repeated (consider transfusing if the patient was anemic with the first echocardiogram). If the results of the cardiac studies normalize, DOXOrubicin may be administered at full dose. If the ECG or other studies do not return to normal within a week, or if cardiac disorders are symptomatic, omit that dose of DOXOrubicin, consult a local cardiologist, and inform the Study Chair. Overt congestive heart failure is an indication for permanent discontinuation of therapy with DOXOrubicin and should be reported to the Study Chair. It is recommended that dexrazoxane not be used on this study. Investigators may use their discretion.

5.8 Pulmonary Abnormalities

Dactinomycin and DOXOrubicin modify tissue response to radiation therapy. The acute onset of tachypnea following administration of these drugs after whole lung radiation may represent radiation

pneumonitis. It is important to seriously consider alternative causes such as Pneumocystis or other infections agents (viral, fungal, bacterial, or mycobacterial) as the cause. Unless radiation pneumonitis can be excluded, further doses of dactinomycin, and DOXOrubicin, should be held until the tachypnea and respiratory symptoms have improved.

5.9 Hepatic Function

5.9.1 Bilirubin

Doses of **DOXOrubicin and dactinomycin** should be modified for an elevated bilirubin according to the following table:

Direct bilirubin	Recommended Dose
< 1.2 mg/dL (< 21 micromoles/L)	Give full dose
1.2-3 mg/dL (21-51 micromoles/L)	Give 50% of scheduled dose
3.1-5 mg/dL (52-86 micromoles/L)	Give 25% of scheduled dose
> 5 mg/dL (>86 micromoles/L)	Hold dose

Doses of **vinCRISTine** should be modified for an elevated bilirubin according to the following table:

Direct bilirubin	Recommended Dose
≤ 3 mg/dL (51 micromoles/L)	Give full dose
> 3 mg/dL (51 micromoles/L)	Give 50% of scheduled dose

5.9.2 Hepatopathy or Sinusoidal Obstruction Syndrome (SOS) (formerly known as veno-occlusive disease of the liver - VOD)

5.9.2.1 Diagnosis

The diagnosis of SOS is made:

By pathologic confirmation by liver biopsy OR
By Doppler ultrasound showing reversal of portal venous flow OR
Clinically, with two or more of the following:
1. Total bilirubin > 1.4 mg/dL (24 micromoles/L)
2. Unexplained weight gain greater than 10% of baseline weight or ascites
3. Hepatomegaly or RUQ pain without other explanation

5.9.2.2 Grading Criteria for Hepatopathy

Mild Hepatopathy	Total bilirubin ≤ 6 mg/dL (≤ 103 micromoles/L) Weight gain of ≤ 5% of baseline of non-cardiac origin Reversible hepatic dysfunction
Moderate Hepatopathy	Total bilirubin > 6 mg/dL (> 103 micromoles/L) and < 20 mg/dL (≤ 342 micromoles/L) Weight gain > 5% of baseline of non-cardiac origin Clinical or image documented ascites Reversible hepatic dysfunction
Severe Hepatopathy	Total bilirubin > 20 mg/dL (> 342 micromoles/L) <u>and/or</u> Ascites compromising respiratory function <u>and/or</u> Renal deterioration <u>and/or</u> Hepatic encephalopathy which may or may not be reversible

5.9.2.3 Therapy Modification for Hepatopathy

Since hepatopathy most likely results from a combination of factors including dactinomycin, DOXOrubicin and vinCRISStine, the following therapy modifications should be taken in the presence of this complication.

Contact Dr. Conrad Fernandez at (902) 470-7290 (or by e-mail Conrad.Fernandez@iwk.nshealth.ca) or Dr. Elizabeth Mullen at (617) 632-5291 to report any severe hepatopathy.

Mild Hepatopathy	Hold hepatotoxic chemotherapy until bilirubin has normalized. The next time the hepatotoxic drug(s) (dactinomycin or DOXOrubicin) most temporally related to the SOS is given, give 50% of the usual dose(s) of that drug(s). If the inciting drug was dactinomycin, consider giving dactinomycin over a 5-day course rather than 1 day. If the patient tolerates the reduced dose, may escalate to full doses of the drug for subsequent courses. Do not discontinue vincristine.
Moderate Hepatopathy	Hold hepatotoxic chemotherapy until bilirubin has normalized. The next time the hepatotoxic drug(s) (dactinomycin or DOXOrubicin) most temporally related to the SOS is given, give 25% of the usual dose(s) of that drug(s). If the inciting drug was dactinomycin, consider giving dactinomycin over a 5-day course rather than 1 day. If the patient tolerates the reduced dose, may gradually escalate to full doses (50% dose then 75% dose then 100% dose) of the drug(s) for subsequent courses. Do not discontinue vincristine.
Severe Hepatopathy	Hold hepatotoxic chemotherapy until bilirubin has normalized. Further use of the inciting agent(s) is at the investigator's discretion. Do not discontinue vincristine (adjust according to vincristine guidelines provided in Section 5.9.1). Notify Study Chair.

5.10 Syndrome of Inappropriate Secretion of Antidiuretic Hormone

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur in association with vinCRISStine. Monitoring of fluid intake and serum sodium concentration is indicated. If the SIADH is severe enough to result in seizures, reduce the next dose of vinCRISStine by 25% and escalate back to 100% if tolerated.

5.11 Impaired Renal Function

Nuclear medicine GFR tests should be performed if the serum creatinine increases by 100% of the baseline value (doubles) or exceeds the upper limit of normal for age. If the GFR falls to less than 50 mL/min/1.73 m², notify the Study Chair. No chemotherapy dose modifications are required for vinCRISStine, dactinomycin or DOXOrubicin based on GFR.

6.0 DRUG INFORMATION

See the consent documents for toxicities. Drug information for vincristine sulfate, dactinomycin, and doxorubicin is provided in the *Drug Information for Commercial Agents used by the Children's Oncology Group* posted on the COG website, available at https://members.childrensoncologygroup.org/prot/reference_materials.asp, under STANDARD SECTIONS FOR PROTOCOLS.

7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

Baseline studies obtained as a part of enrollment on AREN03B2 do not need to be repeated. All other baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. See Section 7.2 for follow-up study schedule.

7.1 Required Clinical, Laboratory and Disease Evaluations Before and During Therapy

7.1.1 Required Observations for Patients on Regimen DD-4A (baseline to tumor progression or relapse)

	Baseline	Before Week 4 (Cycle 2)	Before Week 7 (Cycle 3)	Before Week 10 (Cycle 4)	Before Week 13 (Cycle 5)	Before Week 16 (Cycle 6)	Before Week 19 (Cycle 7)	Before Week 22 (Cycle 8)	Before Week 25 (Cycle 9)	End of treatment	Tumor progression or relapse
History	X	-	-	-	-	-	-	-	-	X	X
Physical Exam (Ht, Wt, BSA, VS)	X	X	X	X	X	X	X	X	X	X	X
Performance Status	X	-	-	-	-	-	-	-	-	X	X
CBC, diff/platelets (1)	X	X	X	X	X	X	X	X	X	X	X
Electrolytes	X	X	X	X	X	X	X	X	X	X	X
Creatinine, SGOT, SGPT, bili (1)	X	X	X	X	X	X	X	X	X	X	X
Total protein/albumin	X	-	-	-	-	-	-	-	-	-	-
Urinalysis	X	-	X	-	X	-	-	-	-	X	X
Pregnancy test (2)	X	-	-	-	-	-	-	-	-	-	-
Abdominal US	X(3)	-	-	-	X(3*)	-	-	X	-	-	X
Chest X-ray	X	-	-	-	X	-	-	X	-	-	X
CT chest	X	-	X(4)	-	-	-	X	-	-	X	X
CT or MRI abdomen/pelvis	X	-	X(5)	-	X(5)	-	-	-	-	X	X
Echocardiogram	X	-	-	-	-	X	-	-	-	X	-
ECG	X	-	-	-	-	-	-	-	-	-	-

Baseline investigations collected to satisfy enrollment on AREN03B2 do not need to be repeated for AREN0532.

(1) Weekly during treatment until Wk 10; after Wk 10, obtain before each cycle.

(2) For females of child bearing potential

(3) At baseline, abdominal US and Doppler recommended but not required to exclude IVC tumor thrombus. (3*) At Wk 13, abd US not required if CT/MRI is used.

(4) Required only for patients with pulmonary relapse from the Very Low risk arm (observation only)

(5) To reevaluate for feasibility for resection only for patients with unresectable disease at diagnosis or at Week 6. Abd US does not need to be done if CT/MRI is used.

Note: Symptomatic patients should have appropriate studies (e.g. Bone scan, MRI head) as clinically indicated.

7.2 Required Clinical, Laboratory and Disease Evaluations after Completion of Therapy

7.2.1 Very Low Risk Stage I Wilms tumor (Surgery alone and observation)

Required Clinical, Laboratory and Disease Evaluations after Study Enrollment

STUDIES TO BE OBTAINED	3 mo	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60	Q2 yrs
History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X(1)
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X(1)
Urinalysis	X	X		X	-	X	-	X	-	X	-	X	-	X	-	X	X(1)
Creatinine, SGOT, SGPT, bilirubin	X	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-
CT chest	X	X	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-
CXR	-	-	X	-	X	-	X	X	X	X	-	X	X	X	X	X	-
CT or MRI abdomen/pelvis	X	X	-	X	-	X	-	-	-	-	-	-	-	-	-	-	-
Abdominal ultrasound	-	-	X	-	X	-	X	X	X	X	-	X	X	X	X	X	-

(1) Until patient is off study.

7.2.2 Standard Risk Stage I and II Wilms tumor with LOH, Standard Risk Stage III Wilms tumor and Stage I Relapsed Very Low Risk patients (Chemotherapy +/- radiotherapy)

Required Clinical, Laboratory and Disease Evaluations after Completion of Therapy

STUDIES TO BE OBTAINED	3 mo	6	9	12	15	18	21	24	27	30	33	36	42	48	54	60	Q2 yrs	
History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X(3)
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X(3)
Urinalysis	X	X		X	-	X	-	X	-	X	-	X	-	X	-	X	X(3)	
Creatinine, SGOT, SGPT, bilirubin	X	X	X	X	-	X	-	X	-	X	-	X	-	X	-	X	-	
Creatinine Clearance (1)	-	-	-	X	-	-	-	X	-	-	-	X	-	X		X	-	
CT chest	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	-	-	
CXR	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	-	
CT or MRI abdomen/pelvis	-	X	-	X	-	X	-	X	-	X	-	X	-	-	-	-	-	
Abdominal ultrasound	X	-	X	-	X	-	X	-	X	-	X	-	X	X	X	X	-	
Echocardiogram/ECG (2)	-	-	-	-	-	-	-	X	-	-	-	-	-	-	-	-	-	

(1) As measured by nuclear GFR or 24-hour urine collection. Required at time of relapse for relapsed Very low risk patients, then annually until patient is off study.

(2) Obtain ECG as clinically indicated.

(3) Until patient is off study.

7.3 Specimens and Data Submissions

Patients must be enrolled on AREN03B2 prior to enrollment/start of therapy on AREN0532; see AREN03B2 for directions on specimen requirements, preparation and shipping directions.

Specimen/Data	Required for participation on AREN0532 study	Refer to Section
Surgical specimen prior to assignment to AREN0532	Yes	Via AREN03B2
Diagnostic imaging studies for central review	Yes	Via AREN03B2
XRT Quality Assurance, including diagnostic images of sites to be irradiated. (Some of these images may already have been submitted via the AREN03B2 study)	Yes for patients receiving XRT	Section 16.9

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from AREN0532 Protocol Therapy

- a) Progressive disease (except for relapse following the surgery and observation only arm for very low risk patients – these patients will remain on protocol).
- b) Second malignant neoplasm.
- c) Refusal of further protocol therapy by patient/parent/guardian.
- d) Completion of planned therapy.
- e) Physician determines it is in patient's best interest.
- f) Found to have Stage III Wilms tumor with combined LOH 1p **and** 16q (will be offered AREN0533 enrollment) (Patient data should be submitted on AREN0532 Week 1-3, and then enrollment on AREN0533 should occur to start therapy at Week 4 on AREN0533).
- g) Found to have any degree of anaplasia at delayed nephrectomy after initial chemotherapy for presumed Stage III favorable histology Wilms (will be offered AREN0321 enrollment).

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

- a) Death.
- b) Lost to follow-up.
- c) Patient enrollment onto another COG study with tumor therapeutic intent (e.g., recurrence).
- d) Withdrawal of consent for any further data submission.
- e) Eighth anniversary of study entry.

9.0 STATISTICAL CONSIDERATIONS

This study is designed to evaluate several risk-based treatment approaches to therapy for patients with very low, low and standard risk favorable histology Wilms tumor. Assessment of outcome will largely be based on comparison of outcome to that seen for similar patients treated on NWTS-5.

9.1 Patient Accrual and Expected Duration of Trial

Protocol accrual is designed to continue until the required number of patients with very low risk favorable histology Wilms tumor (N=115) have been accrued. This is expected to take about 5 years (allowing for a 6-month start-up period for IRB approvals). Patient follow-up for this study is designed to continue for 5 years following the completion of study enrollment.

Very Low Risk: There were about 25 such patients accrued per year on NWTS-5.
Accrual rate: 2 patients per month. Total Expected Accrual: 115 over about 5 years.

Standard Risk: There were about 90-95 such patients accrued per year on NWTS-5.
Accrual Rate: 8 patients per month. Total expected accrual: 485

As of early 2010, the enrollment rate to AREN0532 of patients with very low risk disease was near expected (20 per year). Of the patients enrolled, 92% to date are eligible and 15% of those are very low risk patients. Section 9.2.1 below specifies that 115 eligible patients with very low risk disease are required to meet the study's statistical considerations, and this will require the enrollment of at least 833 patients. In order to assure that the required patients are enrolled, enrollment may continue up to 875 patients.

9.2 Sample Size Considerations and Statistical Analysis Methods

9.2.1 Very Low Risk patients.

The protocol is designed to demonstrate that very low risk patients (Stage I < 2 years of age at diagnosis, favorable histology and tumor weight < 550 g) treated by nephrectomy and observation alone will have a 4-year event-free survival (EFS) $\geq 85\%$ and 4 year overall survival (OS) $\geq 95\%$.

Accrual of patients with very low risk disease is expected to be about 25 per year. The long-term observed event-free and overall survivals for these patients treated with surgery and observation on NWTS-5 were 87% and 98% respectively.¹ If we suppose that a true failure rate of 25% (long-term EFS of 75%) would be unacceptable, then we would need to accrue 115 patients to have 95% power to detect this deficit (testing at the 15% level of statistical significance, 1-sided) (accrual period: about 5 years). This sample size also provides about 95% power (testing at the 15% level of statistical significance, 1-sided) to detect a reduction in the overall survival (from 95% to about 88%).

Monitoring EFS and OS for very low risk patients: The outcome for very low risk patients will be compared to a fixed null hypothesis outcome. EFS will be assumed to plateau at 85%, with those who fail failing exponentially with parameter $\lambda = 1.5$ (95% of all failures occurring prior to 2 years). Survival will be assumed to plateau at 95%, with those who die failing exponentially with parameter $\lambda = 0.75$ (95% of all deaths occurring prior to 4 years).

The method of Woolson (1981) will be used to monitor outcome for this study. Let K be the number of failures observed in the available follow-up and R be the sum of the null cumulative hazard to time t_i , where t_i is the follow-up for patient i . Then $T = K - R$ is approximately normal with independent increments and may be used for interim monitoring using standard group sequential boundaries.

Formal interim analysis of EFS will be done after observing 6 and 12 events (at approximately 33% and 66% of the expected information). Critical p-values for the interim looks (maintaining an overall

significance level of 15%) are 0.045 at the first look, 0.082 at the second look, with the final analysis performed (after the null total of 18 failures have been observed) at a significance level of 0.104. Interim analysis of survival outcome will be performed using the same boundary, with interim looks after 2 and 4 deaths, with the final analysis performed after the null total of 6 deaths have been observed. If there are excess events, this arm will be closed.

Monitoring the rate of metachronous tumor recurrence: For very low risk patients treated with surgery and observation on NWTS-5, the overall rate of metachronous failure was 3/77 (4%). A rate of 4% is assumed acceptable, but a 10% rate is not. The following monitoring rule will be applied: if there are 8 or more failures observed in the contralateral kidney in these 115 patients (observed rate: 7%), the therapy will be considered unacceptable. The chance of declaring the therapy unacceptable would be 9% if the true metachronous tumor rate is 4%, but 90% of the true rate was 10%.

The interim monitoring will be conducted by the COG Phase III Solid Tumor Data and Safety Monitoring Committee. No outcome data (except toxicity information) will be routinely made available to COG Group members while the protocol patients are under active treatment.

9.2.2 Standard Risk patients

The goal is to document an improvement of the NWTS-5 4-year EFS of 75% for patients with Stages I and II favorable histology Wilms tumor with LOH of both 1p **and** 16q by adding doxorubicin (Regimen DD-4A) without radiotherapy to the therapy for these patients who previously received dactinomycin + vincristine only. The number of these patients (Stages I or II; LOH at 1p **and** 16q) to be accrued in a 5-year period is expected to be small (~40) and precludes any formal interim monitoring. The results for these patients will be compared to the results for similar patients treated on NWTS-5.

The goal is to document continued excellent outcome (4 year EFS > 85% and OS > 95%) for patients with Stage III Favorable Histology Wilms Tumor without LOH of 1p **and** 16q treated with vincristine, dactinomycin + doxorubicin + radiotherapy (Regimen DD-4A). Accrual of patients with Stage III, FH tumors without LOH is expected to be about 90-95 per year. The EFS for Stage III, FH tumors without LOH will be compared to that for similar patients who received the same therapy on NWTS-5.

Accrual of Standard Risk patients will continue until the sample size requirement for the very low risk patients has been reached. The biological material provided by these patients will allow investigation and identification of other tumor characteristics that predict for poorer outcome (and consideration of different therapy for those at higher risk of failure).

9.3 **Analysis of Biologic Features of Potential Prognostic Significance**

AREN532 is expected to accrue a total of about 600 patients and we expect to observe about 90 failures. We will be looking at various biologic features of the tumor cells in an attempt to identify factors that are predictive of outcome. While we cannot know ahead of time the prevalence of the various factors to be assessed in this patient population, we can specify the relative risk for which there would be 80% power to detect, given the proportion of patients expected to have the factor.

Proportion of patients with factor of interest	Relative Risk (Factor: no Factor)
0.10	1.96:1.00 Cannot reach 90% power for higher risk in no factor group
0.20	1.75:1.00 1.00:2.41
0.30	1.69:1.00 1.00:1.95
0.40	1.68:1.00 1.00:1.78
0.50	1.70:1.00 1.00:1.70

Assuming the factor identifies patients at higher risk, and all patients treated on this study are at similarly higher risk if they have the factor, then the expected sample size should provide power in excess of 80% to detect a relative risk of at least 2 for such factors, provided they have a prevalence of at least 25% in the population.

9.4 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population (based on an overall accrual of 875 patients) is expected to be:

Accrual Targets			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	44	44	88
Not Hispanic or Latino	420	367	787
Ethnic Category: Total of all subjects	464	411	875
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	19	13	32
Black or African American	97	79	176
Native Hawaiian or other Pacific Islander	1	1	2
White	346	317	663
Racial Category: Total of all subjects	464	411	875

This distribution was derived from patients enrolled on NTWS-5 whose characteristics would have made them eligible for entry onto AREN0532.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

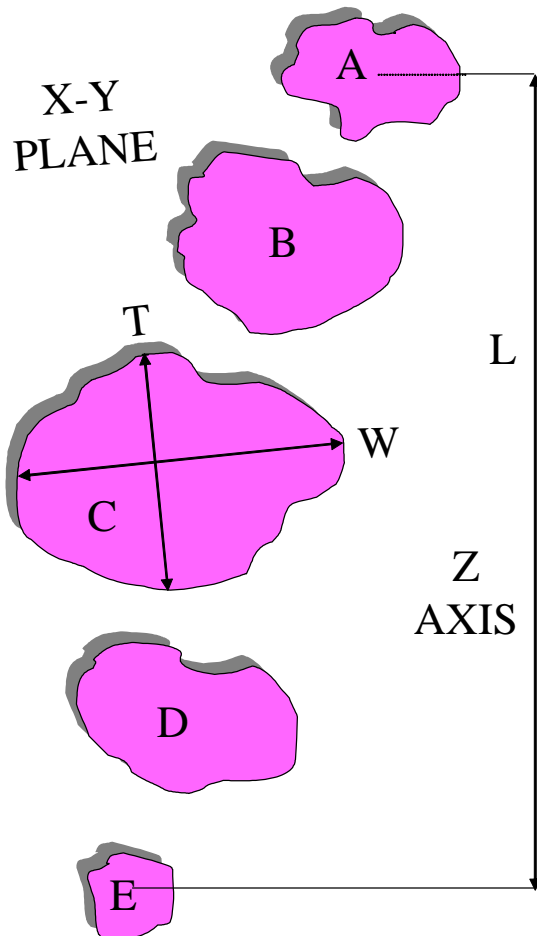
The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting, beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and a copy can be downloaded from the CTEP website (<http://ctep.cancer.gov>).

10.2 Response Criteria

For patients with initially unresectable tumors, this study will use volumetric measurements of the primary tumor using an elliptical model (0.5 times the product of the three largest perpendicular diameters) to assess response to neoadjuvant therapy.

10.2.1 Primary Tumor Measurement

The COG guideline (see diagram) will be used for measurement of tumor masses on cross-sectional imaging (either computed tomography [CT] or magnetic resonance imaging [MRI]).



COG GUIDELINE: TUMOR SIZE MEASUREMENT BASED ON CROSS-SECTIONAL IMAGING

- A, B, C, D, & E are contiguous parallel slices in the X-Y plane (usually axial) showing the tumor
- W and T are the maximal perpendicular diameters on the slice (C in this example) showing the largest surface area
- Tumor length in the Z-axis (L) (perpendicular to X-Y plane) can be obtained either by the [a] (difference in table position of the first and last slices showing the tumor *plus* one *slice* thickness), or [b] the product of ([slice thickness + gap] and the number of slices showing the tumor) *minus* one *gap* distance
- WHO criteria: TxW is used
- RECIST: the larger of the two (T & W) is used (W in this example)
- Elliptical model volume=0.5 LxWxT
- The same modality and measurement method used in the initial imaging should be used in follow ups

TECHNICAL GUIDELINES FOR CROSS-SECTIONAL IMAGING

COMPUTED TOMOGRAPHY (CT)

1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle).
2. CT slice thickness should be 5mm or less.
3. The diameter of a "measurable" mass should be at least twice the reconstructed slice thickness. Smaller masses are considered detectable, but will be counted as "non-measurable."
4. Edge-enhanced lung windows, liver, and bone windows should be photographed, if recorded in hard copies. Digital images are submitted either electronically or in CD using DICOM format.

MAGNETIC RESONANCE IMAGING (MRI)

1. Axial images and at least one additional plane are acquired. At least two pulse sequences, such as T1, T2, STIR, or FLAIR-weighted, or in-phase/out-of-phase images are obtained. Post-contrast images are obtained if appropriate. Measurements should be made using the same sequence best showing the tumor in follow up for comparisons.
2. Only axial images will be used for measurement. The cranio-caudal diameter is represented by the distance between the most cranial and caudal slice positions *plus* one *slice* thickness (or [slice thickness + gap] x number of slices showing the tumor *minus* one *gap* distance).

RELATIONSHIP BETWEEN CHANGE IN SINGLE DIAMETER (RECIST), PRODUCT OF TWO DIAMETERS (WHO), AND THREE PERPENDICULAR DIAMETERS ("VOLUME")
(Modified from Appendix II, Table 2, JNCI 92:213, 2000)

	Diameter, 2R	Product, (2R) ²	Volume, 4/3πR ³
Response	Decrease	Decrease	Decrease
	30%	50%	65%
	50%	75%	87%
Disease Progression	Increase	Increase	Increase
	12%	25%	40%
	20%	44%	73%
	25%	56%	95%
	30%	69%	120%

Target lesions at baseline must measure greater than 1 cm; if these target lesions decrease in size to below 1 cm, care should be taken in measuring and inadvertently progressing a patient due to minimal changes in measurement from a nadir value below 1 cm, which may be within measurement error. When multiple primary or metastatic masses are present, all masses will be described. However, up to 5 target masses should be measured, using the same method in subsequent follow ups.

10.2.2 Tumor Response (Volumetric)

Complete Response (CR): Complete disappearance of the tumor.

Partial Response (PR): At least 64% decrease in volume compared to the measurement obtained at study enrollment.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest disease volume since treatment started.

10.2.3 Response Assessment

Response assessment will pertain only to Stage III patients with unresectable disease at diagnosis.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) the characteristics of the adverse event including the *grade* (severity); 2) the *relationship to the study therapy* (attribution); and 3) the *prior experience* (expectedness) of the adverse event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. In some cases an agent obtained commercially may be used for indications not included in the package label. In addition, NCI may on some occasions distribute commercial supplies for a trial. Even in these cases, the agent is still considered to be a commercial agent and the procedures described below should be followed.

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

- *the current known toxicities for each commercial agent as provided in the Drug Information for Commercial Agents Used by the Children's Oncology Group posted on the COG website; or*
- *the drug package insert.*

11.3 Reporting of Adverse Events for Commercial Agents - AdEERS Abbreviated Pathway

Commercial reporting requirements are provided in Table B. The commercial agent(s) used in this study are listed in the front of this protocol, immediately following the Study Committee roster.

- COG requires the AdEERS report to be submitted **within 5 calendar days** of learning of the event.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Table B

Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

AdEERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days¹

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS
¹ This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is <u>not</u> due to cancer recurrence must be reported via AdEERS.			

As of August 25, 2010, all secondary malignancies should be reported via AdEERS.

11.4 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study-specific adverse events on the COG case report forms and do not affect the requirements for AdEERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include all AdEERS reportable events and all Grade IV or V non-hematological Adverse Events.

12.0 RECORDS AND REPORTING

12.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Pathology Narrative Reports and Surgical Reports. These forms are submitted through the Document Imaging System in the eRDES.
2. Reference Labs' required reports, and QARC data: These data accompany submissions to these centers, which forward their review data electronically to the COG Statistics and Data Center.
3. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and worksheets (essentially paper copies of the RDE screens) provided in the data form packet.

See separate Data Form Packet posted on the COG web site, which includes submission schedule.

12.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

The primary surgical management of pediatric renal tumors including primary nephrectomy and initial biopsy of unresectable Stage III tumors is described in the AREN03B2 Renal Tumors Classification and Banking Study. Enrollment on AREN03B2 is required prior to enrollment on AREN0532.

13.1 Overview

13.1.1 STAGES (detailed staging criteria available in Appendix III)

Stage I	Tumor limited to kidney, completely resected.
Stage II	Tumor extends beyond kidney, completely resected.
Stage III	Residual non-hematogenous tumor present, confined to abdomen, retroperitoneal lymph node involvement. Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen.
Stage IV	Hematogenous metastases (lung, liver, bone, brain) or extra-abdominal LN metastases.
Stage V	Bilateral renal involvement.

13.1.2 Surgical Principles

All surgical specimens removed should be presented to the pathologist fresh or in saline, rather than fixed in formalin. Do Not Bivalve or otherwise disrupt the capsule in OR.

13.1.2.1

Stages I-IV including patients with very low risk Wilms tumor who relapse following initial surgery and observation. (Note: the overall management of Stage IV Favorable Histology Wilms is addressed in AREN0533).

Complete abdominal exploration. A unilateral radical nephrectomy with lymph node sampling via a transperitoneal incision is the surgical procedure. Palpate renal vein and IVC for extension. **Do not biopsy the tumor.** Avoid rupture or spillage by use of an adequate abdominal or thoracoabdominal incision. Flank incisions should not be utilized. Ureter is ligated and divided as low as conveniently possible. Titanium clips used to identify residual tumor. Lymph node sampling should include renal hilar and paraaortic, and/or paracaval nodes as well as any additional suspicious nodes. For tumors deemed inoperable at surgical exploration, open biopsy is obtained.

13.1.2.2

Stage V - Please refer to the bilateral tumor protocol (AREN0534).

13.2 Responsibilities of the Surgeon

Dictated Operative Report including:

- ✓ Demographics (name, date, surgeon, preoperative diagnosis, postoperative diagnosis, operation)
- ✓ Clinical Summary (age, sex, symptoms and brief outline, preoperative treatments, indications and objectives of surgery)
- ✓ Operation-narrative summary (incision, general observations, description of procedure, extent of spread, placement of clips, presence of gross tumor residual, all specimens taken, staging biopsies, and blood loss)

Completed Surgical Checklist Form (in Forms Packet)

Information should be sent as soon as completed to the Statistics and Data Center.

13.3 Nephrectomy for Stage III Wilms Tumor That Were Initially Unresectable at Diagnosis (This procedure should be considered at Week 6 or Week 12.)

Past experience in the NWTSG and the studies conducted by the International Society of Pediatric Oncology have shown that pretreatment with chemotherapy almost always reduces the bulk of the tumor and renders it more safely removed while often allowing preservation of the contiguous organs. However, this method does not result in improved survival rates, and does result in the loss of important staging information. It is recommended therefore that all patients undergo initial exploration to assess operability. It is only then that a tumor biopsy should be considered. Thorough exploration of the abdomen is necessary to detect evidence of extrarenal extension of tumor. If suspicious lymph nodes or other metastatic deposits are found, these should be biopsied to document tumor involvement. Patients who are staged by imaging studies alone are at risk for understaging and overstaging. If pre-nephrectomy therapy is given based on imaging alone, with or without a needle biopsy, the local tumor should be considered to be Stage III.

Patients with initially unresectable tumors will receive chemotherapy and undergo imaging reevaluation after 2 cycles (approximately 6 weeks). If the tumor is deemed resectable at Week 6, the operative procedure can be performed shortly thereafter. A further 6 weeks chemotherapy may be given if still unresectable. Surgical exploration with biopsy confirmation of the original histology is strongly recommended even if still deemed unresectable at Week 12. Serial imaging evaluation is helpful to assess response, but radiographic evidence of persistent disease can occasionally be misleading.

Tumors should be considered unresectable if:

- there is extension of tumor thrombus above the level of the hepatic veins. These patients should be considered for tumor resection when there is evidence of regression of the vena caval thrombus regardless of the degree of response of the primary tumor.
- the tumor involves contiguous structures whereby the only means of removing the kidney tumor requires removal of the other structure (e.g. spleen, pancreas, colon but excluding the adrenal gland). Note however, that Wilms tumors are frequently adherent to adjacent organs. In the majority of cases, there is not frank invasion by the tumor and the organs can be dissected freely from the tumor. Radical en bloc resection, e.g. partial hepatectomy is not generally warranted. If however, removal of a small section of diaphragm, psoas muscle, or tip of the pancreas allows the tumor to be removed intact, this is considered appropriate.
- if it is the surgeons' judgment that nephrectomy would result in significant or unnecessary morbidity/mortality, diffuse tumor spill, or residual tumor.
- if there is pulmonary compromise due to extensive pulmonary metastases.

The operative principles and operative approach is identical to that for a primary unilateral nephrectomy as described in 13.3.1.

13.3.1 Operative Procedure

A generous transabdominal, transperitoneal or thoracoabdominal incision is recommended for adequate exposure. Complete exploration of the abdomen should be performed. A radical nephrectomy is performed with the ureter divided as distally as possible. Routine exploration of the contralateral kidney is not necessary if imaging is satisfactory and does not suggest a bilateral process. (For surgical guidelines for bilateral tumors, please see AREN0534) If the imaging studies are suggestive of a possible lesion on the contralateral kidney, the contralateral kidney should be formally explored to rule out bilateral involvement. This should be done prior to nephrectomy to exclude bilateral Wilms tumor. To do this exploration adequately, the colon and its mesentery should be mobilized from the anterior surface of the contralateral kidney, Gerota's fascia incised, and the kidney turned forward to palpate and visualize both its anterior and posterior surfaces. Any areas suggestive of bilateral involvement should be biopsied. Guidelines regarding the management of children with bilateral Wilms tumor are given in Study AREN0534.

The lateral peritoneal reflection is opened, and the colon is reflected medially. A plane is established outside of Gerota's fascia by sharp and blunt dissection. Before mobilizing the primary tumor, an attempt should be made to dissect, expose and ligate the renal vessels in order to lessen the chance of hematogenous spread of tumor cells while removing the tumor. Preliminary ligation should not be pursued if technically difficult or dangerous. The adrenal gland may be left in place if it is not abutting the tumor; but, if the mass arises in the upper pole of the kidney, the adrenal gland should be removed with the neoplasm. The ureter is ligated and divided as low as conveniently possible, but it is not necessary to remove the ureter completely. The tumor and the uninvolved portion of the kidney are mobilized and removed intact. Any enlarged or suspicious lymph nodes should be included with the specimen. Any suspicious areas that represent metastases should be biopsied, the site(s) identified with small titanium clips so that the locations can be determined later by roentgenograms. The involved areas should be drawn on the diagram in the surgical checklist. The specimen should be specifically identified as to the site from which it was removed.

The use of titanium clips is strongly recommended to identify gross residual tumor. Clips should not be used for hemostasis and those placed for roentgenographic identification or radiation therapy portals should be limited to the minimum number necessary. Metallic clips can interfere with the CT scan. Clips are best applied by placing a non-absorbable suture in the structure to be marked, and attaching the clip to the suture. In general four small clips should be sufficient to delineate the margins of the tumor.

13.3.2 Contiguous Organs

Wilms tumors are frequently adherent to adjacent organs. In the majority of cases, there is not frank invasion by the tumor. Radical en bloc resection, e.g. partial hepatectomy is not generally warranted. Extensive resection including multiple organs, e.g. spleen, pancreas, and colon, is also not advised as this is associated with an increased frequency of complications. If removal of a small section of diaphragm, psoas muscle, or tip of the pancreas allows the tumor to be removed intact, then proceed.

13.3.3 Partial Nephrectomy

Partial nephrectomy is not indicated in the routine patient with unilateral Wilms tumor. Exceptions include children with synchronous or metachronous bilateral disease, or solitary kidneys. The recommended treatment approach for these patients is initial biopsy followed by combination chemotherapy before definitive surgical resection.

A transperitoneal incision is used. Inspect the renal hilar and periaortic area and sample lymph nodes to rule out lymphatic spread. Palpate the renal vein and IVC for evidence of tumor extension. Do not biopsy the tumor if a partial nephrectomy with margins can be performed since this is a criterion for Stage III. Avoid rupture or spillage by use of an adequate incision. Control of the renal vessels is recommended, but

the surgery can be performed without hypothermia or vascular ischemia. In most children, manual compression of the kidney can be used to control bleeding during the dissection. Use of a harmonic scalpel or a similar device may help reduce blood loss and maintain hemostasis. Gerota's fascia is opened and the perirenal fat is dissected off the renal surface excluding the fat attached to the mass. A circumferential incision of the renal capsule around the surface of the tumor should be performed and the capsule peeled back to expose the adjacent renal parenchyma. A wedge or guillotine resection of the tumor is performed. The tumor should be excised with a 0.5 to 1 cm rim of normal parenchyma. After removal of the tumor any bleeding vessels can be suture ligated. If there is transection of the collecting system, a watertight closure with fine absorbable suture is recommended.

During the mobilization of the kidney and during dissection of the tumor, care must be taken not to place traction on the renal vessels. The small vessels in these young patients are prone to intimal injury which can lead to spasm and subsequent thrombosis.

Following any surgical procedure, if the specimen reveals diffuse anaplasia and there is incomplete resection, additional surgery is indicated to ensure complete resection of the tumor.

13.3.4 Lymph Node Documentation

The presence or absence of disease in hilar and regional lymph nodes is an extremely important factor in appropriate treatment. Routine lymph node sampling from the renal hilum and the paracaval or paraaortic areas must be done to guide adequate therapy. Involved or suspicious lymph nodes should be excised. Formal lymph node dissection is not recommended. Label the nodes carefully for separate microscopic examination. All lymph nodes removed should be identified on the surgical check list and the accompanying diagram.

13.4 **Renal Vein/Inferior Vena Cava**

Vascular invasion of the renal vein, cava and atrium presents special surgical challenges. These tumors will often respond to preoperative therapy. Renal vein involvement has been noted in 11% of cases (most often detected at operation) and caval and atria involvement in 5% of Wilms tumor cases. Tumor extension into the renal vein and proximal inferior vena cava can in most cases be removed en-bloc with the kidney. However, primary resection of tumors with extension into the inferior vena cava above the level of the hepatic vein or into the atrium is associated with higher operative morbidity. In these circumstances, preoperative chemotherapy decreases the size and extent of the tumor thrombus without increasing its adherence to the vascular wall, thereby facilitating subsequent excision. Ultrasonographic studies are essential to identify vascular extent of the tumor. The tumor that extends into the renal vein and cava and is "free floating" can usually be simply extracted intact with the kidney specimen. Control of the renal vein and caval above and below the tumor with vessel loops is necessary. The tumor should not be transected. Silk 2-0 stitches can then be placed on either side of the renal vein. This will help with vascular control and limit bleeding. The tumor and kidney should be completely mobilized prior to removing vascular thrombus. A venotomy is then done and the tumor pulled out of the vein. A foley balloon technique can also be used to pull out the tumor. In other instances the tumor may be fixed to the vascular lumen. Extraction is more difficult and a larger venotomy may be required. A similar technique used for removing plaque for a carotid endarterectomy is helpful to lift the tumor off the vein wall. If after preoperative chemotherapy the tumor still extends above the hepatic veins, cardiopulmonary bypass is need to remove the vascular extent of the tumor. The abdominal tumor is mobilized and removed first prior to administration of heparin. After placing the child on bypass the right atrium is opened and the tricuspid valve inspected. The tumor is removed from the heart above and the below at the same time to prevent tumor emboli.

13.5 Tumor Biopsy, Spills and Ruptures

13.5.1 Biopsy

Studies have shown a higher risk of recurrence in patients who had tumor spills or ruptures irrespective of the cause or extent of the soiling. These events result in an increased risk of local recurrence and increased adjuvant therapy with its attendant risks. Tumor biopsy prior to nephrectomy is considered local spill. This results in children receiving additional chemotherapy (doxorubicin) and radiation therapy. Therefore, in very low risk patients with metachronous tumor biopsy should be avoided and renal parenchyma sparing considerations be followed as per Section 13.7.

13.5.2 Tumor Spill and Rupture

Wilms tumor can spill or rupture before and during surgery. This results in soiling of the peritoneal cavity and mandates Stage III therapy. The peritoneum shall be considered "soiled" if there has been:

1. ANY biopsy (either preoperative or intraoperative) in a tumor that is subsequently removed,
2. Preoperative rupture,
3. A tumor spill during surgery, or
4. Separate tumor; nodules on the peritoneal or serosal surfaces are considered a preoperative tumor rupture.

Tumors and adherent tissues that are removed en bloc should produce no tumor spill. However, tumor tissue may be cut across during removal of adherent structures or during removal of lymph nodes. Tumors that are removed in more than one piece, the neoplastic tissue having been cut across in the process, shall be considered to have spilled. Spill would occur if the surgeon transected the renal vein or ureter at the site of tumor extension.

"Rupture" refers to either the spontaneous or post-traumatic rupture of the tumor preoperatively with the result that tumor cells are disseminated throughout the peritoneal cavity. Bloody peritoneal fluid MAY BE considered a sign of rupture. A large amount of blood is unusual and capsular disruption is usually found and must be documented. When a hematoma is present, it is assumed that tumor cells will spread with the blood. Both of these situations are classified as preoperative rupture. Tumor may penetrate the kidney capsule, and the overlying peritoneum, the raw neoplastic tissue surface being in free communication with the peritoneal cavity. If this is found at surgery, it is a sign of preoperative rupture. Peritoneal fluid can be sampled for cytology. However detecting actual malignant cells can be difficult and frequent false positives have been reported. If malignant cells are found, it is suggested that the slides be forwarded to central pathology so that they can be reviewed in conjunction with the treating institution. If cytological analysis of the peritoneal fluid is positive for malignant cells, it is highly suggestive of a preoperative tumor rupture.

All instances of soilage will be classified as Stage III and require abdominal radiation. Flank radiation is given to all Stage III patients with three exceptions (the patients meeting any of these exceptions requiring whole abdominal radiation):

1. Preoperative tumor rupture
2. Peritoneal metastases are found at initial surgery
3. A large intraoperative tumor spill affecting areas outside the tumor bed as determined by the surgeon /treating institution. (Note that it can be difficult to determine the extent of the spill. If the surgeon feels that the spill was confined to the renal tumor bed and controlled immediately, flank RT should be given. If there is concern for more extensive tumor spill, whole abdomen RT should be given (see RT section Table 16.1 b).

All spills, ruptures, and biopsies should be fully described in the operative notes.

Complete description of all techniques is essential. Please provide clear statements regarding how the spill or rupture occurred.

Specifically when tumor extends into the renal vein or inferior vena cava, a precise description of the technique of removal should be given in the operative note. It must be stated in the operative report if the intravascular tumor extension was removed en bloc or if tumor was transected during the resection. It must also be clear whether the tumor thrombus has been removed completely and if there is evidence of either adherence or invasion of the vein wall.

13.6 **Surgical Management of Patients Who Relapse After Primary Nephrectomy and Observation (Very Low Risk Arm)**

13.6.1 Local recurrence

If a child on the AREN0532 very low risk arm (surgery only and observation) relapses with an intraabdominal mass, complete imaging of the abdomen and chest should be obtained to define the extent of recurrence. Recurrence should be confirmed by biopsy (percutaneous or open) and resection if feasible should be performed. Chemotherapy should be given using Regimen DD-4A. If residual intra-abdominal metastatic disease remains after Week 6 of chemotherapy, it should be resected, if complete resection is feasible. If complete resection is not feasible, then continue chemotherapy, with repeat imaging studies at Week 12. The feasibility of resection should again be assessed at that time and resection performed if feasible. If resection is not possible at Week 12, rebiopsy is strongly encouraged. Notify Study Chair.

13.6.2 Metachronous contralateral kidney “relapses”

If a child develops a metachronous tumor, renal sparing surgery should be considered. Notify one of the Study Surgeons (Dr. Bob Shamberger, Dr. Michael Ritchey, Dr. Peter Ehrlich, or Dr. Tom Hamilton). Each tumor should be reviewed by the local surgeon based on the tumor extent to determine the feasibility of renal sparing surgery. We also strongly recommend reviewing the renal sparing surgery protocol in AREN0534, the surgery protocol for Bilateral Wilms tumors and Unilateral High Risk tumors.

13.6.3 Surgical Management of Metastases

13.6.3.1 Intra-abdominal Metastases

Any suspicious site in the abdomen or liver should be biopsied or resected at exploration to determine the nature of the mass as it will affect tumor stage and therapy. If residual intra-abdominal metastatic disease remains at Week 12 of chemotherapy, it should be resected if complete resection is feasible. If complete resection is not feasible, then residual disease should be reassessed for feasibility of resection at the completion of therapy.

13.6.3.2 Pulmonary Metastases

It is strongly recommended that if there is any doubt about the nature of pulmonary nodules that these be biopsied since as many as one third of small (<1 cm) lesions may not be metastatic tumor. All very low risk patients with pulmonary lesions at relapse will receive whole lung radiation. Thus it is critical to define the nature of small pulmonary lesions at relapse.

Most metastases are peripheral and superficial and can be removed thorascopically. For larger lesion (e.g. right middle lobe mass) or for those wishing to perform an open procedure, a standard posterior lateral thoracotomy incision for exploration of the chest can be used. If pulmonary nodules remain after Week 12 of chemotherapy (and irradiation), they should be resected if complete resection is feasible. If complete resection is not feasible, then imaging studies should be repeated at the end of protocol therapy to reassess for feasibility of resection.

13.6.3.3 Bone Metastases

Surgical resection of bone metastases is rarely recommended and should be considered only if such would result in removal of all known disease. Bone metastases are treated with radiation therapy.

13.6.3.4 Brain Metastases

Surgical resection of brain metastases may be considered before the initiation of chemotherapy if complete resection is feasible.

13.7 Surgical Specimens

All surgical specimens removed should be presented to the pathologist fresh or in saline, rather than fixed in formalin. Specimens should be transported to pathology immediately after removal to allow sampling of fresh tissue for molecular and biology studies. Notification of the pathology laboratory in advance will facilitate proper specimen collections. Specific labeling and adequate identification of each specimen removed is most important. Institutions are encouraged to submit samples of metastatic and initially unresectable tumors for central pathology review and banking as part of AREN03B2.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

All patients will already be enrolled on Protocol AREN03B2. Pathology guidelines and specimen requirements are described in AREN03B2. A table summarizing the submission requirements and recommendations in Section 5.1 of AREN03B2 is available at: <https://members.childrensoncologygroup.org/Prot/AREN03B2/AREN03B2Subrequire&recomm.pdf>.

Specimens/materials must be submitted for central review **by Day 7**. In addition to submitting primary tumor material, institutions are encouraged to submit samples of post-chemotherapy tumor samples or recurrent tumor samples as part of the AREN03B2 study.

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

Imaging guidelines are established in AREN03B2. Specific details are provided in that protocol. Digital files must be in Dicom format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Electronic submission of the scans is acceptable via Dicommunicator. Contact QARC at Dicommunicator@QARC.org for further information. Alternative electronic methods, e.g., sFTP are possible. Contact QARC for more information. All imaging studies should be submitted with a copy of the institutional radiologist's report (including the report of the Doppler ultrasound) to:

Quality Assurance Review Center
AREN03B2 Study
640 George Washington Highway, Suite 201
Lincoln, RI 02865
Phone: (401) 753-7600
Fax: (401) 753-7601

16.0 RADIATION THERAPY GUIDELINES

Radiation therapy for patients on Children's Oncology Group (COG) protocols can only be delivered at approved COG RT facilities (COG Administrative Policy 3.9)

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

General Guidelines and Information for the Radiation Oncologist

The radiation therapy guidelines for this study were developed specifically for patients with Stage III favorable histology Wilms tumor (WT) and those with very low risk WT who relapse after initial surgery and observation. Conventional treatment planning and delivery for WT has relied on customized anteroposterior parallel/opposed technique (AP/PA) beam arrangements to define the classical flank, whole-abdomen and whole-lung irradiation volumes. Even in the era of 3-dimensional conformal radiation therapy and intensity-modulated radiation therapy methods, the same classic fields and beam arrangements are preferred provided that treatment field design is based on cross-sectional imaging (CT) acquired at the time of simulation. The authors of these guidelines request that the radiation oncologist use CT-based treatment planning to define the field or volume for treatment and critical normal tissue structures.

Required Benchmarks and Questionnaires

CT-based conventional (beams defined by bony anatomy rather than by a contoured target volume) radiation therapy using photons or electrons, 3D-conformal (3DCRT) or intensity-modulated radiation therapy (IMRT) using photons will be allowed on this study. Patients may not receive intraoperative radiation therapy or proton therapy on this protocol. Centers participating in this protocol using 3DCRT are required to complete the 3D benchmark; those using IMRT must complete the IMRT questionnaire and benchmark or phantom. Benchmark materials and questionnaires may be obtained from the Quality Assurance Review Center (www.qarc.org) and must be submitted before patients on this protocol can be evaluated. Contact the RPC for information regarding their IMRT phantoms (<http://rpc.mdanderson.org/rpc>).

Guidelines and Requirements for the Use of IMRT

Investigators using IMRT will be required to comply with the guidelines developed for the use of IMRT in National Cancer Institute sponsored cooperative group trials. These guidelines are available through www.qarc.org. These guidelines require that protocol explicitly state their requirements and methods for localization and immobilization; the use of volumetric imaging; target and organ motion management; nomenclature, definitions and rationale for targets and organs at risk; target volume coverage and normal tissue dose constraints; effects of heterogeneity in tissues; and quality assurance.

16.1 Indications for Radiation Therapy

Table 16.1 a Indications for radiation therapy

Favorable histology at the time of initial presentation	Abdominal Stage III tumors
Favorable histology at the time of relapse	(1) Local relapse regardless of extent of resection (2) Pulmonary relapse (3) Metachronous relapse in the remaining kidney with involved surgical margins or lymph nodes or spillage (4) Any distant relapse sites as indicated in Table 16.1 b.

Table 16.1 b Radiation dose and volume by tumor stage or clinical presentation

Treatment Site	Clinical Presentation and Dose	
Flank irradiation Patients with residual tumor will receive supplemental irradiation with 10.8Gy.	Stage III favorable histology	10.8Gy
	Recurrent Wilms tumor	10.8Gy
Whole abdomen irradiation (WAI) Patients with residual tumor will receive supplemental irradiation with 10.5Gy.	Abdominal Stage III a) Preoperative tumor rupture* b) Peritoneal metastases are found at initial surgery c) A large intraoperative tumor spill outside the tumor bed as determined by the surgeon/treating institution	10.5Gy
	Abdominal Stage III (a) Diffuse unresectable peritoneal implants	21Gy
Metachronous Wilms tumor	Negative surgical margins	No RT
	Microscopically involved margins or nodes	10.8Gy
	a) Preoperative tumor rupture* b) Peritoneal metastases are found at surgery c) A large intraoperative tumor spill outside the tumor bed as determined by the surgeon/treating institution	Follow WAI guidelines
	Microscopically involved margins after partial nephrectomy in a patient with progressive disease after 3-drug chemotherapy	14.4Gy
	Gross residual disease after partial resection or biopsy	21.6Gy
Whole lung irradiation	Lung metastases	10.5Gy; Age < 12 months
		12Gy; Age ≥ 12 months
Whole brain irradiation	Brain metastases	21.6Gy followed by local boost of 10.8Gy; Age < 16 years
		30.6Gy; Age ≥ 16 years
Liver irradiation (1) Patients with residual tumor will receive supplemental irradiation with 5.4-10.8Gy.	Focal metastases	19.8Gy
	Diffuse metastases	19.8Gy
Bone irradiation	Bone metastases	25.2Gy; Age < 16 years
		30.6Gy; Age ≥ 16 years
Lymph node irradiation	Resected LN metastases	10.8Gy
	Unresected LN metastases	19.8Gy

*Preoperative Tumor Rupture includes spontaneous or posttraumatic rupture. A large amount of bloody peritoneal fluid and positive cytology are highly suggestive of a preoperative rupture.

16.1.1 Tailoring fields by site

Unless constrained in meeting target volume coverage requirements and organ at risk dose recommendations, the dose to the entire vertebral body should be uniform to avoid growth asymmetry.

16.1.2 Timing of radiation therapy

When indicated, radiation therapy shall begin concurrent with the initiation of chemotherapy after surgery. Radiation therapy will begin at Week 1 and as close to the beginning of chemotherapy as possible when the primary tumor is initially resected. It is preferred that radiation therapy start by Day 10 and no later than Day 14, unless medically contraindicated; surgery is designated as Day 0. If initial surgery is delayed, radiation therapy should begin after recovery from the surgery when chemotherapy is reinitiated. When indicated, very low risk patients who relapse should have radiation therapy delivered at the start of retrieval therapy.

16.1.3 Criteria to start radiation therapy

There are no specific contraindications to starting radiation therapy on this protocol unless the patient is deemed medically unstable by the treating physicians.

16.2 **Emergency Irradiation**

Patients are not expected to require emergency irradiation on this protocol.

16.3 **Equipment**

X-rays with a nominal energy between 4 and 15 MV, inclusive. When 3DCRT or IMRT are used and the path of any beam traverses lung tissue, 10 MV or less should be used. In the unusual circumstance of a superficial lesion, electron fields may be used. Conventional, 3DCRT, and IMRT methods are allowed. Patients may not receive intraoperative radiation therapy or proton beam therapy on this study.

Calibration: The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

CT treatment planning: All patients will undergo CT treatment planning for this protocol. Slices no more than 5 mm thick (2-3 mm is recommended) shall be taken throughout the extent of the irradiated volume.

16.4 **Target Volume Definitions**

CT-based beam's eye view treatment planning and classical (parallel-opposed treatment portals) field design will be sufficient for most patients treated on this study. When using 3D-CRT or IMRT, however, target volumes will be defined according to International Commission on Radiation Units and Measurements (www.icru.org) Report-50 and 62 definitions for gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). One exception is the GTV that may be defined as the gross residual tumor *and/or* tumor bed. This differs from the ICRU 50 definitions where the GTV defines only the gross residual tumor. The clinical target volume (CTV) is anatomically confined margin surrounding the GTV and is intended to treat microscopic disease. For this study, the CTV margin will be 1cm for primary and 0.5cm for supplemental treatment. Supplemental treatment is defined as boost irradiation of residual disease. The PTV is a geometric expansion of the CTV in 3-dimensions and is not anatomically confined. The purpose of the PTV is to account for uncertainty in immobilization and daily variability in patient positioning. For this study, the PTV margin will be institutionally defined and may range from 0.5 to 1cm.

Patients treated on this protocol may receive conventional, 3DCRT/IMRT or a combination of all methods. For consistency in reporting, the designations of GTV1, CTV1 and PTV1 will be used when volumetric targeting is used for the initial phase of radiation therapy. GTV2, CTV2 and PTV2 will refer to target volumes in supplemental (boost) irradiation of residual disease.

16.4.1 Motion Management and Margins to Account for Target Volume and Organ Motion

Considering motion of normal tissues and target volumes is important. The internal target volume (ITV) is defined as the CTV surrounded by the IM component of the PTV and is meant to account for potential motion of the CTV. The planning organ at risk volume (PRV) includes the organ at risk surrounded by a margin to compensate for physiologic change in the target volume. If adequate clinical data do not exist to define the IM component of the PTV or the PRV margin, the following suggestions are provided:

- A margin of at least 0.5cm should be added to any organ at risk to form the PRV.
- For a CTV susceptible to physiologic motion, a margin of at least 0.5cm should be added to the CTV prior to PTV margin expansion or a PTV margin of at least 1.0cm should be chosen.
- For tumors of the thorax or abdomen, an assessment should be made to determine the extent of motion present. PTV margins should include this motion as a component.
- IMRT may be used for tumors of the thorax only if the degree of tumor motion is assessed and can be limited to 0.5cm in any direction. If required to achieve this goal, techniques for managing or suppressing tumor motion shall be applied.
- A description of the method used and evidence of the remaining tumor motion (i.e., observed motion during fluoroscopy, motion of surrogate markers using camera systems, or analysis of 4D CT) should be submitted on the Motion Management Reporting Form with the Quality Assurance Documentation materials as noted in Section 16.9.

16.4.2 Flank irradiation

16.4.2.1 Primary Wilms tumor

This is a classic treatment volume that may or may not include para-aortic lymph node irradiation. The dose guidelines are included in Section 16.1, Table 16.1 b. The treatment volume should be approached AP/PA with parallel-opposed beams unless alternative beams arrangements are required to spare the contralateral kidney. The treatment field design is determined by the CT/MR scan at initial presentation before administration of chemotherapy and includes the outline of the kidney and associated tumor with a 1cm margin. In patients with ureteral extension and Stage III disease, the inferior border of the flank irradiation field should be placed approximately 1cm below the level of disease in the ureter (after discussion with the surgeon), especially if this extension is below the level of the kidney. The superior, inferior and lateral borders of the radiation therapy field should be placed at the edge of targeted volume, approximately 1cm from the kidney and tumor volume at initial presentation. The medial border of the treatment field should be extended across the midline to include all of the vertebral bodies (with a margin of 1cm beyond the vertebral body) at the level of concern but should not overlap any portion of the contralateral kidney. In patients with tumors that extend into the contralateral flank without tumor invasion of the contralateral kidney, the addition of a 1cm margin to the medial tumor extent might include a significant volume of the contralateral kidney. For these patients, no more than 1cm margin beyond the vertebral body is required. In the presence of tumor thrombus involving the IVC, the flank irradiation treatment volume should include the entire thrombus with a 1cm margin.

When it has been determined that lymph nodes are pathologically involved with tumor, the entire length of the para-aortic lymph node chain should be included in the treatment volume. The upper border should be the crus of the diaphragm and the lower border the bottom of L₅. Because lymph node irradiation is a component of flank irradiation, the treatment volume should be approached AP/PA with parallel-opposed beams unless alternative beams arrangements are required to spare the contralateral kidney.

16.4.2.2 Recurrent Wilms tumor

The dose guidelines are included in Section 16.1, Table 16.1 b. The treatment volume should be approached AP/PA with parallel-opposed beams unless alternative beams arrangements are required to

spare the contralateral kidney. The treatment field design is determined by the tumor outline (CT/MR scan) at the time of recurrence PRIOR to any chemotherapy or surgery with a 1cm margin. The superior, inferior and lateral borders of the radiation therapy field should be placed at the edge of targeted volume, approximately 1cm from the initial recurrent tumor volume. The medial border of the treatment field should be extended across the midline to include all of the vertebral bodies (with a margin of 1cm beyond the vertebral body) at the level of concern but should not overlap any portion of the contralateral kidney. In patients with tumors that extend into the contralateral flank without tumor invasion of the contralateral kidney, the addition of a 1cm margin to the medial tumor extent might include a significant volume of the contralateral kidney. For these patients, no more than 1cm margin beyond the vertebral body is required. In the presence of tumor thrombus involving the IVC, the flank irradiation treatment volume should include the entire thrombus with a 1cm margin.

When it has been determined that lymph nodes are pathologically involved with tumor, the entire length of the para-aortic lymph node chain should be included in the treatment volume. The upper border should be the crus of the diaphragm and the lower border the bottom of L₅. Because lymph node irradiation is a component of flank irradiation, the treatment volume should be approached AP/PA with parallel-opposed beams unless alternative beams arrangements are required to spare the contralateral kidney.

16.4.3 Whole Abdomen Irradiation (Primary and recurrent Wilms tumor)

This is a classic treatment volume; dose guidelines are included in Section 16.1, Table 16.1 b. The treatment volume should be approached AP/PA with parallel-opposed beams unless alternative beams arrangements are required to spare normal tissue. The treatment field design shall encompass the entire peritoneal cavity that extends from the dome of the diaphragm superiorly to the pelvic diaphragm inferiorly. The lateral borders are the abdominal walls. The superior border shall be placed approximately 1cm above the dome of the diaphragm. The inferior border shall be placed at the bottom of the obturator foramen. The lateral borders of the field will be placed approximately 1 cm beyond the lateral abdominal wall. The femoral heads and portions of the heart (beyond a 1cm margin from the diaphragm) should be shielded using customized blocking with cerrobend or multileaf collimator.

Supplemental (boost) irradiation is required for patients with gross-residual disease after surgery including those with unresected lymph nodes that meet radiological criteria for involvement. Target volumes and doses are defined in Sections 16.4.4 and 16.1, respectively.

16.4.4 Supplemental (“boost”) irradiation

Supplemental irradiation (10.8Gy) is required after flank or whole abdominal irradiation for gross residual tumor. The use of 3DCRT or IMRT is preferred. Three-dimensional imaging data should be acquired with the patient in the treatment position to define a GTV, CTV, PTV and critical structures. The GTV is the postoperative residual tumor and should be based on imaging performed for treatment planning. The CTV will be an anatomically confined margin of 0.5cm surrounding the GTV. The PTV will be a geometrically expanded margin surrounding the CTV. The PTV margin will be chosen by the local institution, ranging from 0.5-1cm. When 3-dimensional treatment planning is not available, the residual tumor will be targeted with a field-edge margin of 1cm.

16.4.5 Metachronous Wilms tumor after contralateral nephrectomy

In children with metachronous Wilms tumor developing in the remaining kidney, adjuvant radiation therapy is not indicated when partial nephrectomy has been performed and there is no evidence of residual tumor (no imaging evidence to suggest tumor and pathologically negative surgical margins), lymph node involvement or tumor spillage. **The use of a percutaneous or open surgical biopsy alone does not qualify a child with a metachronous Wilms tumor for flank irradiation;** however, if the surgical margins are involved with tumor then flank irradiation (10.8Gy) is recommended. If microscopically involved margins are present after partial nephrectomy in a tumor that demonstrated progression after 3-

drug chemotherapy then a higher flank irradiation dose (14.4Gy) will be indicated. The target volumes for metachronous Wilms tumor are similar to the flank irradiation fields as defined as in Section 16.4.2. If there is gross residual or unresectable Wilms tumor in the remaining kidney, the total recommended dose is 21.6Gy (14.4 + 7.2Gy). The supplemental dose of 7.2Gy should be administered using the guidelines in Section 16.4.4.

16.4.6 Small-field renal sparing conformal irradiation

In special clinical situations, *small-field* conformal renal sparing irradiation may be indicated to conserve remaining renal parenchyma. The likely clinical situation is one in which the contralateral kidney has been removed and there are indications for radiation therapy in the remaining ipsilateral kidney after chemotherapy and surgery. The purpose of *small-field* irradiation is to avert rendering the patient anephric. 3DCRT or IMRT is required and IMRT may be preferred for renal hilar lesions as described with other indications below:

- Microscopically involved tumor margins after multiple surgical attempts in a salvageable (functioning) kidney. The tumor should be of the favorable histologic type and must have demonstrated a good response to chemotherapy.
- Residual tumor in the renal hilum that cannot be resected without sacrificing the kidney. The tumor should be of the favorable histologic type and must have demonstrated a good response to chemotherapy.

Small field renal sparing conformal irradiation **SHOULD NOT** be used for patients with any of the following adverse prognostic features after chemotherapy and/or surgery:

- a) unfavorable histologic type
- b) lymph node involvement
- c) local or diffuse tumor spillage
- d) blastemal predominant tumors
- e) no CT/MRI response to 3-drug chemotherapy regimen
- f) progressive disease after chemotherapy

The GTV will be defined as the surgical bed (involved margins) and/or gross-residual residual tumor (renal hilar tumor) based on the postchemotherapy and postoperative evaluations with CT/MRI. It is highly recommended that the GTV be determined in consultation with the surgeon. An anatomically-confined margin of 1cm is added to the GTV to create the CTV. A geometric margin of 1cm is added to the CTV to create the PTV. A dose of 10.8Gy will be prescribed for most indications described above; however, a dose of 21.6Gy is recommended when there is gross residual tumor after a partial resection or biopsy, as in the case of an unresectable renal hilar tumor. An AP/PA conformal technique is recommended for polar tumors (upper or lower pole) while multifield 3DCRT or IMRT is preferred for renal hilar tumors.

Children with metachronous Wilms tumor who require small-field renal sparing RT techniques (3DCRT or IMRT) must have all imaging and 3D/IMRT treatment plans sent to QARC for preapproval before initiating RT.

16.4.7 Whole lung irradiation

This is a classic treatment volume and dose guidelines are included in Section 16.1, Table 16.1 b. Both lungs are irradiated regardless of the number and location of metastases. The targeted volume includes the entire lung volume, mediastinum and the pleural recesses. The superior, inferior and lateral borders of the treatment fields should be placed 1cm beyond the defined volume. The inferior extent of the anterior and posterior costo-diaphragmatic recesses of the pleural cavity may be determined by lateral radiograph of the chest with the patient in a supine position and arms elevated. Beam's eye view treatment planning is

preferred and careful review of the sagittal and coronal views of the cost-diaphragmatic recesses should help determine the inferior extent of the pleural cavity. By necessity, the whole lung irradiation field irradiates the upper abdomen; often the inferior border is located at the L-1 vertebral body level. The humeral heads and associated joint spaces should be shielded. If a patient requires both whole lung and either flank or whole-abdomen irradiation, all treatment volumes should be treated concurrently.

16.4.8 Liver irradiation

Radiation therapy is not indicated if, at the time of initial presentation, and prior to the administration of chemotherapy, the following conditions are met: the liver metastasis is determined to be solitary by CT or MR and surgical exploration and the metastasis has been resected with negative margins.

Radiation therapy is indicated for all remaining settings that include metastatic disease involving the liver. The entire liver shall be irradiated to 19.8Gy if the liver is diffusely involved with metastatic disease. The dose guidelines are included in Section 16.1, Table 16.1 b. If the entire liver volume is not involved, the individual metastases should be irradiated with a 2cm margin based on the residual tumor, imaging abnormality at the time of treatment planning. The site(s) of resected metastases will require RT if the margins are positive. In the setting of complete response to chemotherapy, the investigator will be required to administer RT to the metastatic site using a 2cm margin based on the prechemotherapy volume. Supplemental irradiation of hepatic metastatic disease beyond 19.8Gy may be administered to limited volumes (< 75% of the entire liver) at the discretion of the radiation oncologist. The suggested dose range should be 5.4 to 10.8Gy. There are no margin or technique requirements. While irradiating the liver, the dose to the upper pole of the remaining kidney should be monitored. A posterior kidney block may be inserted in order to limit the dose to the remaining kidney to ≤ 14.4 Gy. An anteroposterior parallel/opposed technique (AP/PA) is recommended for liver irradiation.

Liver regeneration occurs after surgery in patients who undergo hepatic resection. Regenerating hepatic tissues are especially vulnerable to radiation. Radiation therapy should be withheld in patients undergoing resection until Day 10 after surgery (surgery is considered Day 0). For patients who have undergone hepatic resection, radiation therapy should not be initiated when the values of ALT and AST are greater than ten times the upper limit of normal, as defined institutionally. Liver function tests (ALT and AST) should be repeated at the time 12 weeks after the initiation of radiation therapy.

16.4.9 Brain irradiation

In patients with brain metastases, the whole brain is included in the irradiation field to a dose of 21.6Gy or 30.6Gy (see Section 16.1, Table 16.1 b). When the whole brain dose is 30.6Gy, no additional boost irradiation is required. However, if the whole brain dose is 21.6Gy, a boost of at least 10.8Gy is required. In patients with ≤ 3 circumscribed lesions especially in patients younger than 3 years, a limited volume (tumor, or tumor bed only with 0.5cm margin) boost dose of 10.8Gy in 6 fractions using 3DCRT or IMRT may be administered after whole brain irradiation to 21.6Gy.

A lateral parallel-opposed technique (right and left lateral) is recommended for whole brain irradiation.

16.4.10 Bone irradiation

In patients with bone metastasis, the GTV (lesion on bone scan or CT/MRI scan) with a margin of at least 1cm is included in the irradiation volume. The entire bone need not be irradiated. An anteroposterior parallel/opposed technique (AP/PA) is recommended for bone irradiation. The bone irradiation dose is shown in Section 16.1, Table 16.1 b.

16.4.11 Lymph node irradiation

Lymph nodes with metastatic tumor, meeting radiologic criteria for pathologic involvement, that have not been surgically removed, should receive radiation therapy to 19.8Gy. The treatment volume should include

the entire involved group of lymph nodes (abdomen or chest etc.) at the time of initial presentation. When conventional treatment techniques are used, the field borders should allow a margin of at least 1cm on the imaging defined abnormality and the entire vertebral body should be included in the irradiated volume, where applicable. An anteroposterior parallel/opposed technique (AP/PA) is recommended for lymph node irradiation.

16.5 Target Dose

The daily dose to the prescription points (conventionally planned cases) or volumes (volumetric planning based on a PTV) should be 1.8Gy in all sites except when large volumes are irradiated, such as in whole lung (1.5Gy) and whole abdomen irradiation (1.5Gy). Please refer to Section 16.1, Table 16.1 b for the recommended total dose by site. The following table lists equivalent doses for different dose-fractionation schemes:

Nominal Dose (Gy)	Dose/fraction	Number of Fractions
10 Gy	1.8 Gy	6
	1.5 Gy	7
	2 Gy	5
20 Gy	1.8 Gy	11
	1.5 Gy	14
	2 Gy	10

16.5.1 Prescribed dose

If conventional planning methods are used, the prescription point should be at or near the centroid of the target volume. If 3DCRT or IMRT is used, dose should be prescribed to an isodose surface that encompasses the PTV and allows the dose uniformity requirements to be satisfied as noted in Section 16.5.5. The dose may be prescribed to the isocenter or to the midplane in the majority of patients who will be treated using parallel opposed (anterior or lateral) irradiation fields.

16.5.2 Conformal boost

When a conformal boost is indicated as in patients with gross residual disease in the abdomen or in patients with brain metastases, the dose shall be prescribed to an isodose surface that encompasses the PTV. The dose uniformity requirements in Section 16.5.5 shall be satisfied.

16.5.3 Dose definition

Dose is to be specified in centigray (cGy)-to-muscle.

16.5.4 Tissue heterogeneity

Heterogeneity corrections will not be made for whole lung irradiation but are required for all other treatments whether or not the beam path subtends lung tissue. Heterogeneity corrections are required even when conventional planning methods are used and shall be applied for IMRT in compliance with current guidelines for the use of IMRT in clinical trials (guidelines available at www.QARC.org). When IMRT is used in lung, the heterogeneity correction algorithm must be approved by QARC. For questions about heterogeneity corrections or approved algorithms, please contact QARC (www.QARC.org).

16.5.5 Dose uniformity

For treatment plans using conventionally defined beams, the dose variations in the targeted volume shall be within +7%, -5% of the prescription-point dose. For volume-based treatment plans, the entire PTV should be encompassed within the 95% isodose surface and no more than 10% of the PTV should receive greater than 110% of the prescription dose as evaluated by dose volume histogram.

16.5.6 Interruptions, delays, and dose modifications

There will be no planned rests or breaks from treatment and, once radiation therapy has been initiated, treatment will not be interrupted except for severe hematologic toxicity defined as ANC < 300/ μ L or platelets less than 40,000/ μ L during the course of treatment. Under these circumstances, radiation therapy shall be delayed until the counts have recovered. Blood product support should be instituted according to institutional/protocol guidelines. The reason for any interruptions greater than three treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. When interruptions or delays occur, the total number of fractions or cumulative dose should be modified according to the tables below (when the administered dose per fraction is 2Gy, similar prescription guidelines as shown below for 1.5Gy and 1.8Gy are to be followed):

Planned Prescribed Dose = 10.8Gy

Treatment Interruption	Fractional Dose(Gy)	Fraction Number	Cumulative Dose (Gy)
0 - 3 day break	1.8	6	10.8
	1.5	7	10.5
4 - 7 day break	1.8	7	12.6
	1.5	8	12.0
> 7 day break	1.8	8	14.4
	1.5	9	13.5

Planned Prescribed Dose = 19.8Gy

Treatment Interruption	Fractional Dose (Gy)	Fraction Number	Cumulative Dose (Gy)
0 - 3 day break	1.8	11	19.8
	1.5	14	21
4 - 7 day break	1.8	12	21.6
	1.5	15	22.5
> 7 day break	1.8	13	23.4
	1.5	16	24

16.6 Treatment Technique

Beam Configuration: Every attempt should be made to minimize dose to organs at risk without compromising coverage of the target volume. For flank, whole abdomen, whole lung, whole brain irradiation, whole liver and some metastatic sites, parallel-opposed techniques are preferred. For supplemental irradiation (boost treatments), although simple opposed field plans are acceptable, the use of oblique fields, or 3-dimensional conformal therapy (coplanar or non-coplanar), or IMRT is encouraged to minimize dose to normal surrounding structures.

16.6.1 Patient position

The patient may be treated in the supine or prone position. Appropriate sedation/anesthesia and/or immobilization devices shall be used.

16.6.2 Field shaping

Field shaping shall be done with customized cerrobend blocking, which is at least 5 HVL thick, or a multi-leaf collimator.

16.7 Organs at Risk

The organ at risk guidelines in this section are recommendations. If the recommended doses to the organs at risk are exceeded because of target volume coverage requirements or other conditions, an explanation should be included in the quality assurance documentation. In some cases, IMRT may be the preferred treatment method to meet these recommendations and the required target volume coverage guidelines.

Organ	Dose (Gy)
Kidney-whole	14.4 Gy
Kidney-partial (50%)	19.8 Gy
Liver-whole	23.4 Gy
Liver-partial (50%)	30.6 Gy
Lung-whole	12.0 Gy
Lung (when PTV occupies > ½ bilateral lung volume)	15.0 Gy
Lung (when PTV occupies < ½ bilateral lung volume)	18.0 Gy

When the whole abdomen or liver dose exceeds 14.4 Gy, the renal dose should be limited to 14.4 Gy by using appropriate renal shielding. Several techniques may be used for renal shielding when the WAI dose is > 14.4Gy. The use of posterior partial transmission kidney blocks for the entire course of treatment is recommended. The thickness of the block will be determined by the treatment plan. The dimensions of the block should be 5 mm wider than the projection of the kidney on a PA digitally reconstructed radiograph.

16.8 Dose Calculations and Reporting

If 3D conformal techniques are used to treat patients on this study, a 3D benchmark needs to be completed and submitted to QARC. Institutions treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org). Contact the RPC (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms. Patients will be considered unevaluable if approved benchmarks are not on file at QARC.

16.8.1 Prescribed dose

The monitor units required to deliver the prescribed dose shall be calculated and submitted using the *RT-1/IMRT Dosimetry Summary* form. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry. The total prescribed dose shall be calculated and reported on the RT-2 Radiotherapy Total Dose Record form. If 3DCRT or IMRT is used, dose should be prescribed to an isodose surface that encompasses the PTV and allows the dose uniformity requirements to be satisfied

16.8.2 Normal tissue dosimetry

The daily dose to the critical organs should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and reported on the *RT-2 Radiotherapy Total Dose Record* form. For patients treated with volume-based techniques, the appropriate dose-volume histograms should be submitted and *RT-1/IMRT Dosimetry Summary* form completed. If IMRT is used, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

Table 16.8.2 a Required normal tissue DVH data according to treatment site(s)

Treatment Area	Required DVH
Neck	Thyroid
Chest	Right lung
	Left lung
	Heart
Abdomen	Liver
	Right kidney
	Left kidney

16.9 Quality Assurance Documentation

Within three days of the start of radiation therapy, detailed treatment data shall be submitted for on treatment review of the primary site and lung; only the RT-2 form and a copy of the radiotherapy record (treatment chart) need to be submitted for the metastatic site(s). **Children with metachronous bilateral Wilms tumor who require small-field renal sparing RT techniques (3DCRT or IMRT) must have all imaging and 3D/IMRT treatment plans sent to QARC for preapproval before initiating RT.**

Digital Submission:

Submission of treatment plans in digital format (either DICOM RT or RTOG format) is required. Digital data must include CT scans, structures, plan, and dose files. Submission may be by either sFTP or CD. Instructions for data submission are on the QARC web site at www.qarc.org under "Digital Data." Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via sFTP or submitted separately. Screen captures are preferred to hard copy for items that are not part of the digital plan.

Please submit the following for the Primary Site Target Volume:

Treatment Planning System Output:

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. This shall include GTV1, CTV1, and PTV1, when volumetric targeting is used for the primary component of treatment and GTV2, CTV2, and PTV2 when supplemental irradiation is administered. A DVH shall be submitted for the organs at risk specified in Section 16.8. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup images are sufficient.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data:

- Copies of all diagnostic imaging studies in DICOM format and reports along with the surgical and pathology reports used in defining the target volume.
- Copies of verification images for each field.
- Documentation of an independent check of the calculated dose when IMRT is used.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the QARC and the radiation oncology reviewers.
- If emergency RT is administered, documentation should be provided in the form of the RT-2 Total Dose Record Form and the radiotherapy record (treatment chart).

Forms:

- RT-1/IMRT Dosimetry Summary Form.
- Motion Management Reporting Form (if applicable, see Section 16.4.1).

Within 1 week of the completion of radiotherapy, the following data shall be submitted for all patients:

- RT-2 Radiotherapy Total Dose Record Form.
- Radiotherapy record (treatment chart) including prescription and daily and cumulative doses to all required areas and organs at risk.

Note: For metastatic sites other than lung only, an RT-2 form with a copy of the treatment chart should be submitted within 1 week following completion of treatment.

Electronic submission via sFTP for all data is preferred. Alternatively, the supportive data and forms may be sent to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Dosimetry and Physics Question should be directed to:
QARC Protocol Dosimetrist
Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

16.10 Definitions of Deviation in Protocol Performance

16.10.1 Prescription dose

Minor Deviation: The prescribed dose differs from that in the protocol by between 6% and 10%.

Major Deviation: The prescribed dose differs from that in the protocol by more than 10%.

16.10.2 Dose uniformity

Minor deviations for 3D conformal and IMRT treatments:

The entire PTV is not encompassed within the isodose surface representing 95% of the prescription dose or more than 10% of the PTV receives more than 110% of the prescription dose.

Minor deviations for 2D treatments:

The dose variation in the treated volume is not within +7%, -5% of the prescription point dose.

16.10.3 Volume

Minor Deviation: Margins less than specified or fields excessively large as deemed by the study reviewer.

Major Deviation: A portion of the tumor (GTV) or potentially tumor bearing area (CTV) is not included in the treated volume.

16.10.4 Critical structures

A minor or major deviation will be assessed at the time of data review (depending on the details of each case) if the critical structure dose limits are exceeded.

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria					
Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II: SUPPORTIVE CARE GUIDELINES

These are provided for institutional consideration. Investigator discretion should be used, and individual considerations made for specific patient situations and institutional practices.

Venous Access

A central venous catheter (single lumen port or externalized line) for Regimen DD-4A is recommended prior to initiation of therapy.

Prophylactic Antibiotics

The risk of PCP pneumonia is low on the DD-4A regimen. If the physician chooses to use medications to prevent *Pneumocystis Carinii* pneumonia Trimethoprim/Sulfamethoxazole (75 mg/m² of trimethoprim per dose) BID should be administered on two or three consecutive days of the week. Alternatives including aerosolized or intravenous pentamidine, oral dapsone, or oral atovaquone may be considered if the patient does not tolerate trimethoprim/sulfamethoxazole.

Anti-emetics

Anti-emetics should be administered with chemotherapy. The preferred agents are ondansetron or granisetron.

Constipation

The frequency of bowel movements should be monitored during vinCRISTine therapy. Laxatives/stool softeners should be provided per institutional practice.

Growth Factors

Myeloid growth factor support is not recommended for Regimen DD-4A. Myeloid growth factors may be given at the discretion of the treating physician but should be recorded on the data forms.

Blood Product Support

Irradiation

Blood products should be irradiated following the current FDA guidelines found at:

<http://www.fda.gov/cber/gdlns/gamma.htm>

Investigators in Canadian institutions need to follow the CSA standards for Blood and Blood Components CAN/CSA-Z902-04 issued in March 2004 and available at <http://www.shopcsa.ca>.

Further supportive care guidelines may be obtained from: Supportive Care of Children with Cancer, 2004 ed., Arnold Altman, M.D.

APPENDIX III: STAGING

For Wilms tumor, rhabdoid tumor of the kidney, clear cell sarcoma of the kidney:

Stage I - Tumor limited to kidney, completely resected. The renal capsule is intact. The tumor was not ruptured or biopsied prior to removal. The vessels of the renal sinus are not involved. There is no evidence of tumor at or beyond the margins of resection. NOTE: For a tumor to qualify for certain therapeutic protocols as Stage I, regional lymph nodes must be examined microscopically.

Stage II - The tumor is completely resected and there is no evidence of tumor at or beyond the margins of resection. The tumor extends beyond kidney, as is evidenced by any one of the following criteria:

- There is regional extension of the tumor (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus, as discussed below)
- Blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumor.

Note: Rupture of spillage confined to the flank, including biopsy of the tumor, is no longer included in Stage II and is now included in Stage III.

Stage III - Residual non-hematogenous tumor present following surgery, and confined to abdomen.

Any one of the following may occur:

- Lymph nodes within the abdomen or pelvis are involved by tumor. (Lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for Stage IV),
- The tumor has penetrated through the peritoneal surface,
- Tumor implants are found on the peritoneal surface,
- Gross or microscopic tumor remains post-operatively (e.g., tumor cells are found at the margin of surgical resection on microscopic examination),
- The tumor is not completely resectable because of local infiltration into vital structures,
- Tumor spillage occurring either before or during surgery,
- The tumor is treated with preoperative chemotherapy (with or without a biopsy regardless of type- tru-cut, open or fine needle aspiration) before removal,
- Tumor is removed in greater than one piece (e.g. tumor cells are found in a separately excised adrenal gland; a tumor thrombus within the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumor within vena cava into thoracic vena cava and heart is considered Stage III, rather than Stage IV even though outside the abdomen.

Stage IV - Hematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdomino-pelvic region are present. (The presence of tumor within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).

Stage V - Bilateral renal involvement by tumor is present at diagnosis. An attempt should be made to stage each side according to the above criteria on the basis of the extent of disease.

APPENDIX IV: INFORMATION SHEETS REGARDING RESEARCH STUDY AREN0532 — DD-4A

**INFORMATION SHEET REGARDING RESEARCH STUDY AREN0532 — DD-4A
(for children 7 through 12 years of age)**

A New Chemotherapy Study for Children with Standard Risk Wilms Tumor

1. We have found that you have a tumor called a Wilms tumor. A Wilms tumor is a type of cancer that grows in your kidneys.
2. We are asking you to take part in a research study about Wilms tumor. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat children with Wilms tumor. Most children with Wilms tumor have an operation (called surgery) to take out the tumor, and then get two chemotherapy drugs (special medicines to kill the cancer). Some children get radiation therapy as well (powerful x-rays directed at the tumor location). This treatment works well for many children. But, in some children, the tumor comes back after treatment.
3. Children with Wilms tumor who are part of this study will be treated with two standard chemotherapy drugs, plus another drug to see if three drugs work better than two drugs to help keep the cancer from coming back. Some children may also get radiation therapy. During and after your treatment, you will be checked regularly in the clinic to see how you feel and how well the drugs are working.

Something called a central line is often used to give children anti-cancer medicines. A central line is a small tube that is put into a large vein in your chest. Medicines are then given through the central line instead of with a needle. Also, blood samples can be taken through the central line, so you should not need to have a needle stick.

4. Sometimes, good things can happen to people when they are in a research study. These good things are called “benefits”. We hope that a benefit to you of being part of this study is that the new treatment will be better at getting rid of the tumor than the normal treatment, but we do not know for sure if there is any benefit of being part of this study.
5. Sometimes, bad things can happen to people when they are in a research study. These bad things are called “risks”. The risks to you from this study are that the new treatment will not be better than the normal treatment at getting rid of the cancer. Other things may happen to you that we do not yet know about.
6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY AREN0532 — DD-4A
(for teens from 13 through 17 years of age)

A New Chemotherapy Study for Teens with Standard Risk Wilms Tumor

1. We have found that you have a cancer called a Wilms tumor. A Wilms tumor is a cancer that grows in your kidneys. The type of Wilms tumor that you have is considered “standard risk”.
2. We are asking you to take part in a research study about Wilms tumor. A research study is when doctors work together to try out new ways to help people who are sick. In this study, we are trying to learn more about how to treat children and teens with Wilms tumor. Most people with Wilms tumor have an operation (called surgery) to take out the tumor, and then get two chemotherapy drugs (special medicines to kill the cancer). Some children and teens get radiation therapy as well (powerful x-rays directed at the tumor location). This treatment works well for many children and teens. But, in some people, the tumor comes back after treatment.
3. Children and teens with standard risk Wilms tumor who are part of this study will be treated with two standard chemotherapy drugs, plus another drug to see if three drugs work better than two drugs to help keep the cancer from coming back. Some people may also get radiation therapy, if their tumor has spread to other sites. During and after your treatment, you will be checked regularly in the clinic to see how you feel and how well the drugs are working.

Something called a central line is often used for people getting chemotherapy. A central line is a special type of tubing that is put into a large vein in your chest. Medicines are then given through the central line instead of with a needle. If you have a central line you should not have to get poked to get chemotherapy or to have blood samples taken.

4. Sometimes, good things can happen to people when they are in a research study. These good things are called “benefits”. We hope that a benefit to you of being part of this study is that the new treatment will be better at getting rid of the tumor than the standard treatment, but we do not know for sure if there is any benefit of being part of this study.
5. Sometimes, bad things can happen to people when they are in a research study. These bad things are called “risks”. The risks to you from this study are that the new treatment will not be any better than the standard treatment at getting rid of the cancer. Another risk is that you may have more side effects from the chemotherapy, if you are treated with three drugs instead of two. Other things may happen to you that we do not yet know about.
6. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Make sure to ask your doctors any questions that you have.

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SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM-SURGERY ONLY AND OBSERVATION

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

Treatment for Very Low Risk Favorable Histology Wilms Tumor Surgery Only and Observation

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say “you” in this consent form, we mean you or your child; “we” means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You are being asked to join this part of the study because you have a favorable histology Wilms tumor that has some risk of returning after treatment. We know this because you have enrolled on the Wilms tumor biology study AREN03B2. This biology study looks at and studies your tumor cells, the images of the tumor and its location in the body. Study doctors also do some tests to find out the genetic make-up of your tumor. Your study doctor can tell you these details about your tumor and its stage (staging means knowing where the tumor started and whether it has spread to other areas of the body).

It is common to enroll children and adolescents with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for your disease and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage you to include your child in the discussion and decision to the extent that she or he is able to understand and take part.

WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS DISEASE?

The current usual treatment for children less than 2 years old with a small Stage I tumor is surgical removal of the kidney followed by chemotherapy with either one drug (vincristine) or two drugs (vincristine and dactinomycin). In about 95% of children this treatment will get rid of the cancer.

WHY IS THIS STUDY BEING DONE?

The overall goal of this part of the study is to find out if children less than 2 years old with a small Stage I Wilms tumor can be safely treated with surgery alone followed by careful observation. Chemotherapy has potential immediate and longer term side effects, so study doctors would like to find out if not giving chemotherapy is a safe approach. We think that for about 85% of children surgery alone will get rid of the cancer, without chemotherapy. These children will avoid short and long term side effects from chemotherapy. We think that 10-15% of children cared for by surgery alone will likely have their tumor return sometime in the first two years after surgery. This is called relapse or recurrence. The chances are good that for most of these children we can still get rid of the cancer. However they will need more intensive treatment with chemotherapy and radiation therapy (treatment with high energy X-rays).

Also, treatment information from this study will be linked to the tumor samples collected as part of the AREN03B2 study. Researchers hope that they will be able to tell if any other biological or genetic factors can help predict the best treatment for patients with these renal tumors.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

The total number of people enrolled on AREN0532 is expected to be between 600 and 875.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

You will not receive chemotherapy on this arm of the study. This is the experimental part of the research. You will be watched very closely for any sign that the tumor has come back. You will be asked to see your doctor according to the following schedule:

Very Low Risk Stage I Wilms tumor (Surgery alone and observation)

What will be done:	How often:
History and Physical exam	Every three months for the first three years after enrollment Every six months for the next two years, then every two years
Urinalysis	At three, six, and twelve months after enrollment Every six months for the next two years Every year for the next two years, then every two years
Blood tests	Every three months for the first year after enrollment Every six months for the next two years Every year for the next two years
CT chest	At 3, 6, 12, and 18 months following surgery.
Chest X-ray	At 9, 15, 21, 24, 27, and 30 months after surgery then every 6 months for two and a half years.
CT or MRI abdomen/pelvis	At 3, 6, 12, and 18 months following surgery.
Abdominal ultrasound	At 9, 15, 21, 24, 27, and 30 months after surgery, then every six months for two and a half years

RESEARCH STUDY TESTS AND PROCEDURES

Four CT scans of the chest and abdomen will be done after surgery as part of this research protocol. For children not taking part in this research, treating institutions vary in the exact number and type of scans used in follow up. All the other tests and procedures you will get are part of regular cancer care

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to get follow-up as shown above. As this is a new approach to this tumor type, it is very important that the follow up plan is carefully followed. In the first five years, we want to make sure the tumor has not come back. Previous experience with surgery-only suggests that if the tumor returns, most of the tumors will have come back by 2 years after the surgery. COG would like to continue to find out about your health for about eight years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after surgery helps us understand the long-term effects of the study.

If the Wilms tumor comes back while you are on this study, your doctor will discuss the options of treatment available. This study recommends treatment with DD-4A (a standard combination of three chemotherapy drugs) and radiation treatment. You will be asked to sign a separate consent form to receive this treatment. Information on how your child is doing with this treatment will continue to be sent to COG.

Your doctor or the researcher may decide to stop observation alone under the following circumstances:

- if new information becomes available that shows that another treatment would be better for the person

You can stop taking part at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

The biggest risk to you from having surgery only is that if the tumor comes back, you will need intensive chemotherapy, and maybe radiation therapy, to get rid of the disease. For very young subjects, risks from the drugs may be worse, or may not appear until later in life.

The risks of surgery will be explained to you by your surgeon when you sign the consent for the procedure.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from taking part in this clinical trial, but we cannot be certain. You may benefit from not having chemotherapy since there can be side effects and late effects from chemotherapy. *Late effects are side effects of treatment that happen later in life. These effects include such things as slow growth, inability to have children, or another cancer.*

We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- **Current standard therapy (surgery, and then chemotherapy with vincristine and, perhaps, dactinomycin)**
- **Taking part in another clinical trial**

Please talk to your doctor about these and other options.

WHAT ABOUT PRIVACY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about this certificate is in Attachment #1 of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this Hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. There are no plans to pay you for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care. You may stop being in the study at any time. If you stop being in the study, you will not be penalized and you will not lose any benefits to which you are entitled. Physicians and hospital personnel will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research-related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at ###-###-####.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at ###-###-####.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at ###-###-####.

WHERE CAN I GET MORE INFORMATION?

The *Family Handbook for Children with Cancer* has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org

If you are in the United States you may call the NCI's *Cancer Information Service* at 1-800-4-CANCER (1-800-422-6237)

Visit the *NCI's Web site* at <http://www.cancer.gov>

Visit the *COG Web site* at <http://www.curesearch.org>

Information about long term follow-up after cancer treatment can be found at <http://www.survivorshipguidelines.org/>

A description of this clinical trial will be available at: <http://www.ClinicalTrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

SIGNATURE

I have been given a copy of all _____ [insert total number of pages] pages of this form.
The form includes one (1) attachment.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant _____ Date _____

Parent/Guardian _____ Date _____

Parent/Guardian _____ Date _____

Physician/PNP obtaining consent _____ Date _____
IRB# _____ IRB Approved: _____

Attachment #1
Information about the Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

**SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM-RELAPSE
FOLLOWING OBSERVATION ONLY**

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

**Treatment for Children who relapse following Observation Only for Very Low Risk
Favorable Histology Wilms Tumor**

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say “you” in this consent form, we mean you or your child; “we” means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

When your child was diagnosed with Wilms tumor, we asked you to take part in a study to find out if your child's cancer could be treated with surgery only and without chemotherapy. You agreed to take part in that study. Subjects who have their tumor come back after treatment with surgery need further treatment with chemotherapy. You are being asked to take part in this study because you have a favorable histology Wilms tumor that has returned after observation alone. As part of the study, chemotherapy will be given to treat the Wilms tumor that has grown back. Your study doctor can tell you these details about your tumor and its stage (staging means knowing where the tumor started and whether it has spread to other areas of the body).

It is common to enroll children, adolescents and young adults with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for your disease and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage you to include your child in the discussion and decision to the extent that she or he is able to understand and take part.

**WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS
DISEASE?**

The most common treatment for relapse after observation of very low risk favorable histology Wilms tumor depends upon the location of the relapse. If the relapse is in the original site of the tumor or other parts of the body except the remaining kidney, surgery to remove as much tumor as possible is undertaken. Then, treatment occurs with anti-cancer drugs (chemotherapy), vincristine, dactinomycin and doxorubicin for a period of about 25 weeks at the same time as treatment with high energy x-rays (radiation therapy).

If the relapse is in the remaining kidney, then anti-cancer drugs (chemotherapy), vincristine, dactinomycin and doxorubicin may be given to first shrink the tumor, then surgery to remove as much of the tumor as possible. The total length of the chemotherapy is 25 weeks. Radiation therapy is not routinely planned for this situation.

WHY IS THIS STUDY BEING DONE?

This part of AREN0532 is for subjects who have:

- Relapsed after observation of Very low Risk Wilms tumor.

We plan to treat subjects on this arm of the study in several ways:

Subjects with local or distant relapse not involving the opposite kidney will get therapy that contains the three standard drugs (vincristine, dactinomycin and doxorubicin). This is called Regimen DD-4A. Therapy will be given over a period of about 25 weeks. Radiation therapy will be given to sites of metastatic tumor at the start of chemotherapy. Regimen DD-4A is used for other higher risk Wilms tumors.

Subjects with relapse in the remaining kidney will get standard therapy with Regimen DD-4A but no radiation therapy unless we are unable to fully remove the relapsed tumor.

The overall goal of this study is:

- **to confirm that these strategies that have been used in the past for relapse after observation alone are effective.**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

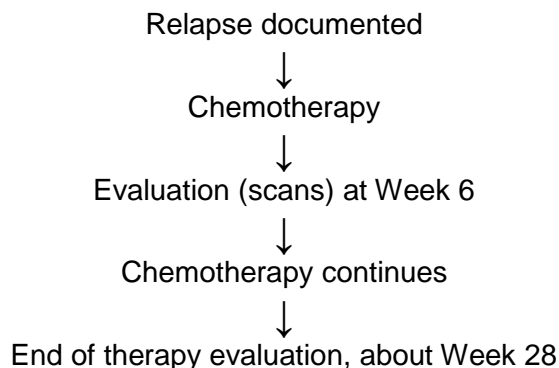
The total number of people enrolled on AREN0532 is expected to be between 600 and 875.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Treatment Plan

The treatment plan used on this part of the study is considered standard for relapse in this situation. The research part of the study is to collect information that will confirm previous observations that this is an effective strategy.

Diagram of DD-4A treatment



Treatment Plan Table for Regimen DD-4A:

<i>Drug</i>	<i>How the drug will be given</i>	<i>Days</i>	<i>Week</i>
Vincristine	IV over 1 minute*	On Day 1	1-10,13,16,19,22,25
Dactinomycin	IV over 1-5 minutes	On Day 1	1,7,13,19,25
Doxorubicin	IV over 15-120 minutes	On Day 1	4,10,16,22

* Vincristine can be given over one minute or using a minibag over several minutes by some institutions.

Subjects (people on this study) with local or distant relapse not involving the opposite kidney will receive radiation therapy. Radiation therapy is not routinely planned for subjects with a relapse in the remaining kidney.

RESEARCH STUDY TESTS AND PROCEDURES

No additional tests or procedures will be done because you already consented to research tests when you signed the consent for the Observation part of the study. Standard tests and procedures are described in Attachment #1.

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to get treatment on this study over a period of about 25 weeks if on Regimen DD-4A. After treatment, subjects will have follow-up examinations and medical tests for about eight years. COG would like to continue to find out about your health for about eight years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after you complete treatment helps us understand the long-term effects of the study

Your doctor or the researcher may decide to take you off this protocol therapy under the following circumstances:

- if he/she believes that it is in your best interest
- if the disease grows larger during treatment on this study
- if you have side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

There are no additional treatment risks associated with this study. These are standard treatments for relapse in this situation. We will continue to collect information about how well your child responds to treatment.

Treatment Risks

All people who get cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications. **For very young subjects, risks from the drugs may be worse, or may not appear until later in life.**

Common side effects include nausea, vomiting, hair loss, mucositis and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy. The risks of the individual drugs given as standard treatment and risks of radiation therapy are listed on the tables in **Attachment #2**. Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in your Family Handbook for Children with Cancer. You will be taught more about caring for your child when his or her blood counts are low.

There is a risk that the treatment plan will not get rid of the cancer or that the cancer can go away after the treatment and then come back at a later date.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- **Current standard therapy without being on this study**
- **Taking part in another clinical trial**

Please talk to your doctor about these and other options.

WHAT ABOUT PRIVACY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about this certificate is in Attachment #3 of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this Hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. There are no plans to pay you for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care. You may stop being in the study at any time. If you stop being in the study, you will not be penalized and you will not lose any benefits to which you are entitled. Physicians and hospital personnel will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research-related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at ###-###-####.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at ###-###-####.

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at ###-###-####.

WHERE CAN I GET MORE INFORMATION?

The *Family Handbook for Children with Cancer* has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org

If you are in the United States you may call the NCI's *Cancer Information Service* at 1-800-4-CANCER (1-800-422-6237)

Visit the *NCI's Web site* at <http://www.cancer.gov>

Visit the *COG Web site* at <http://www.curesearch.org>

Information about long term follow-up after cancer treatment can be found at <http://www.survivorshipguidelines.org/>

A description of this clinical trial will be available at: <http://www.ClinicalTrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

SIGNATURE

I have been given a copy of all _____ [insert total number of pages] pages of this form. The form includes three (3) attachments.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant _____ Date _____

Parent/Guardian _____ Date _____

Parent/Guardian _____ Date _____

Physician/PNP obtaining consent _____ Date _____
IRB# _____ IRB Approved: _____

Attachment #1
Treatment and Procedures Common to all Patients with Wilms Tumor

Central Line

For drugs to be given by vein, your doctor will likely recommend that you have a central venous line placed. A description of the types of central lines is in your Oncology Family Notebook.

Methods for Giving Drugs

Various methods will be used to give drugs to patients. The drugs on this study will be given using a needle or tubing inserted into a vein (**IV**).

Standard DD-4A Therapy:

<i>Drug</i>	<i>How the drug will be given</i>	<i>Days</i>	<i>Week</i>
Vincristine	IV over 1 minute*	On Day 1	1-10, 13, 16, 19, 22, 25
Dactinomycin	IV over 1-5 minutes	On Day 1	1, 7, 13, 19, 25
Doxorubicin	IV over 15-120 minutes	On Day 1	4, 10, 16, 22

* Vincristine can be given over one minute or using a minibag over several minutes by some institutions.

Radiation therapy is delivered during the first few days of the treatment schedule.

Standard tests and procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study:

- Frequent labs to monitor blood counts and blood chemistries
- Urine tests to measure how the kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins
- X-rays and scans to monitor the patient's response to treatment
- Tests to monitor heart and lung functioning

Standard tests and procedures that will be done to follow your progress after the study therapy is done are listed below:

What will be done:	How often:
History and Physical exam	Every three months for 3 years Every six months for the next two years then every two years [#]
Urinalysis	At three and six months after completion of treatment Every six months until 3 years Every year until 5 years then every two years [#]
Blood tests	Every 3 months for 1 year Every six months until 3 years Every year until 5 years.
Nuclear or urine test for kidney function	Every year for five years after completion of treatment
CT chest	Every 6 months for 3 years beginning 6 months after completion of treatment
Chest X-ray	Every 6 months for 5 years beginning 3 months after completion of treatment
CT or MRI abdomen/pelvis	Every 6 months for 3 years beginning 6 months after completion of treatment
Abdominal ultrasound	Every 6 months for 5 years beginning 3 months after completion of treatment
ECG/Echocardiogram*	At 2 years after completion of treatment

[#] Until we stop collecting medical information about you.

* If your doctor thinks you need these tests.

Attachment #2

Risks of Chemotherapy Drugs and Radiation Therapy

Risks and side effects related to dactinomycin include those which are:

Likely	Less Likely	Rare But Serious
<ul style="list-style-type: none"> • Nausea • Vomiting • Temporary hair loss • Fewer white blood cells, red blood cells and platelets in the blood. <ul style="list-style-type: none"> ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily 	<ul style="list-style-type: none"> • Inflammation and/or ulceration (rarely) of the lips, the mouth, throat, esophagus, intestines or rectum • Fever • Diarrhea and/or abdominal pain • Damage to the skin if the medication leaks from a vein • Elevation in the blood of certain enzymes found in the liver which could indicate liver irritation or damage • Loss of appetite • Redness, burning or a darkening of the skin at sites which have received radiation in the past • A feeling of extreme tiredness, weakness or not feeling well • Muscle aches and pains • Acne or other types of skin bumps • Lower levels of calcium in the blood • A slowing of normal growth 	<ul style="list-style-type: none"> • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen which makes it look larger. • Inflammation of the lungs which could lead to chest pain and discomfort • A new cancer or leukemia resulting from this treatment

Risks and side effects related to vincristine include those which are:

Likely	Less Likely	Rare But Serious
<ul style="list-style-type: none"> • Hair loss • Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes • Constipation 	<ul style="list-style-type: none"> • Jaw pain • Headache • Muscle weakness • Pain and bloating in your abdomen • Numbness and tingling • Wrist or foot drop • Drooping eyelids • Double vision, difficulty seeing at night • Hoarseness of your voice • Difficulty sweating • Abnormal walk with foot slapping • Difficulty with urination or increase desire to urinate • Dizziness and low blood pressure when you stand • Abnormal hormone function which may lower the level of salt in the blood • A mild drop in white blood cells, red blood cells and platelets in the blood <ul style="list-style-type: none"> ○ a low number of red blood cells can make you feel tired and weak ○ a low number of white blood cells can make it easier to get infections ○ a low number of platelets causes you to bruise and bleed more easily 	<ul style="list-style-type: none"> • Complete stoppage of your intestinal activity which can result in intestinal blockage • If the drug leaks out of the vein when being administered it will cause damage to nearby tissue • Seizures • Vocal cord paralysis • Difficulty breathing • Inability to walk • Decreased ability to hear clearly • Damage to the nerve to the eye (optic nerve) leading to decreased vision and possible blindness • In combination with other chemotherapy drugs: damage to the liver which can lead to inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger

Risks and side effects related to doxorubicin include those which are:

Likely	Less Likely	Rare But Serious
<ul style="list-style-type: none"> • Nausea • Vomiting • Temporary hair loss • Pink or red color to urine, sweat, tears, saliva • Fewer white blood cells, red blood cells and platelets in the blood. <ul style="list-style-type: none"> ○ A low number of red blood cells can make you feel tired and weak 	<ul style="list-style-type: none"> • Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores) • Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid • Facial flushing 	<ul style="list-style-type: none"> • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Ulceration of the lower intestinal tract • An irregular heart beat which can be life-threatening • Severe damage to the heart muscle which may lead to

<ul style="list-style-type: none"> ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily ● Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function 	<ul style="list-style-type: none"> ● Fever/chills ● Hives ● High levels of uric acid in the blood which could damage the kidneys ● Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed. ● Damage to the skin if the medication leaks from a vein ● Thickening and hardening of the veins through which the medication is given ● Reddening reaction of the vein through which the drug is given. ● Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage. ● Tearing and inflammation of the eyes ● Loss of appetite ● Redness and burning at sites which have received radiation in the past ● Diarrhea 	<ul style="list-style-type: none"> ● severe heart failure ● A new cancer or leukemia resulting from this treatment.
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The risk of heart damage may be greater in very young children than in older ones.

Radiation Therapy risks:

The radiation oncologist will discuss in detail the risks involved with radiation therapy when you sign the consent for the radiation therapy. The radiation oncologist will show you which part of the body will receive radiation therapy. In general, the side effects of radiation therapy are limited to the site of treatment and may include: temporary hair loss, nausea, vomiting, diarrhea, redness or dryness of the skin, low blood counts, mouth sores and/or injury to tissues or organs that may be included in the treatment field. Sterility may be associated with ovarian or testicular irradiation.

Potential late effects of radiation therapy may include problems with soft tissue or bone growth, vision problems, changes in endocrine function (low hormone levels), learning disabilities or brain injury, and increased risk for developing another cancer. These late effects depend on which part of the body receives radiation therapy, the age of the patient, and the drugs and surgery given at the same time as part of the therapy.

Attachment #3
Information about the Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

SAMPLE RESEARCH INFORMED CONSENT/PARENTAL PERMISSION FORM- CHEMOTHERAPY ARM

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Institutions should use the sections of this document which are in bold type in their entirety. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to any of the sections in bold type, they must be justified in writing by the investigator at the time of the institutional audit.

Treatment for Standard Risk Favorable Histology Wilms Tumor Chemotherapy arm

If you are a parent or legal guardian of a child who may take part in this study, permission from you is required. The assent (agreement) of your child may also be required. When we say “you” in this consent form, we mean you or your child; “we” means the doctors and other staff.

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS STUDY?

This study is called a clinical trial. A clinical trial is a research study involving treatment of a disease in human patients. This study is organized by Children's Oncology Group (COG). COG is an international research group that conducts clinical trials for children with cancer. More than 200 hospitals in North America, Australia, New Zealand, and Europe are members of COG.

You are being asked to take part in this study because you have a favorable histology Wilms tumor that has some risk of returning after treatment. We know this because you have enrolled on the Wilms tumor biology study AREN03B2. This biology study looks at and studies your tumor cells, the images of the tumor and its location in the body. Study doctors also do some tests to find out the genetic make-up of your tumor. They are looking especially for a genetic change called loss of heterozygosity (LOH). Your study doctor can tell you these details about your tumor and its stage (staging means knowing where the tumor started and whether it has spread to other areas of the body).

It is common to enroll children, adolescents and young adults with cancer in a clinical trial that seeks to improve cancer treatment over time. Clinical trials include only people who choose to take part. You have a choice between a standard treatment for your disease and this clinical trial.

Please take your time to make your decision. Discuss it with your friends and family. We encourage you to include your child in the discussion and decision to the extent that she or he is able to understand and take part.

WHAT IS THE CURRENT STANDARD OF TREATMENT FOR THIS DISEASE?

The most common treatment for low and standard risk favorable histology Wilms tumor is surgery to remove as much tumor as possible, and then treatment with anti-cancer drugs (chemotherapy), vincristine and dactinomycin, for a period of about 19 weeks and, perhaps, treatment with high energy x-rays (radiation therapy).

WHY IS THIS STUDY BEING DONE?

This part of AREN0532 is for subjects who have:

- Stage I or II Wilms tumor that is large, with the LOH change, or subject is more than 24 months old.
- Stage III Wilms tumor that is without the LOH change

Your doctor can explain the details of size and genetic changes to you.

We plan to treat subjects on this arm of the study in several ways:

Subjects with Stage I or II Wilms tumor and no LOH change will not be treated on this study. The usual treatment for these patients is with two standard drugs (vincristine and dactinomycin).

Subjects with Stage I or II Wilms tumor who have the LOH change will get therapy that contains the two standard drugs (vincristine and dactinomycin) with another drug added, doxorubicin. This is called Regimen DD-4A. Therapy will be given over a period of about 25 weeks. Radiation therapy will not be given. Regimen DD-4A is used for other higher risk Wilms tumors. Using Regimen DD-4A for Stage I or II Wilms tumor with the LOH change is experimental. We think that if we give more treatment to these subjects, by adding doxorubicin, there is a better chance that we can get rid of the cancer for as long as possible.

Subjects with Stage III Wilms tumor who do not have the LOH change will get standard therapy with Regimen DD-4A and radiation therapy.

The overall goal of this study is:

- **to find out if some subjects with a higher risk of having their tumor return (Stage I or II Wilms tumor with the LOH change) will benefit from the addition of doxorubicin to the current standard treatment regimen. This is experimental treatment.**
- **to find out if there are things about the tumor cells other than the LOH change that might tell us why standard treatment does not get rid of the tumor for Stage III Wilms tumor subjects without the LOH change.**

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

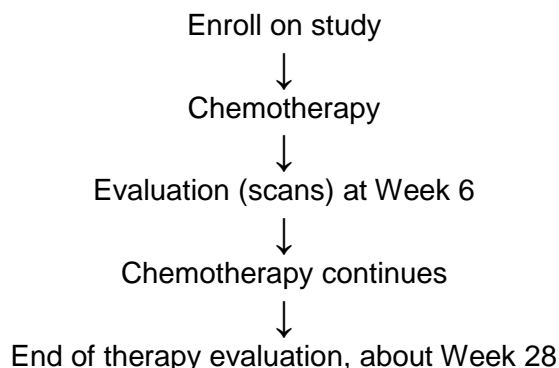
The total number of people enrolled on AREN0532 is expected to be between 600 and 875.

WHAT WILL HAPPEN ON THIS STUDY THAT IS RESEARCH?

Treatment Plan

Subjects with Stage I or II Wilms tumor who have the LOH change will have had chemotherapy (usually vincristine and dactinomycin) for a few weeks before the LOH is found. They will be switched to a more intensive treatment lasting a period of about 25 weeks with the two standard drugs vincristine and dactinomycin plus the drug doxorubicin. This is called Regimen DD-4A. Radiation therapy will not be given. The research part of the study is to see if adding doxorubicin will make the cancer go away for as long as possible.

Diagram of DD-4A treatment



Treatment Plan Table for Regimen DD-4A: Stage I and II subjects with LOH will start at Week 4.

<i>Drug</i>	<i>How the drug will be given</i>	<i>Days</i>	<i>Week</i>
Vincristine	IV over 1 minute*	On Day 1	1-10,13,16,19,22,25
Dactinomycin	IV over 1-5 minutes	On Day 1	1,7,13,19,25
Doxorubicin	IV over 15-120 minutes	On Day 1	4,10,16,22

* Vincristine can be given over one minute or using a minibag over several minutes by some institutions.

1. Subjects with Stage III Wilms tumor who do not have the LOH change will get standard therapy with Regimen DD-4A as above for a period of about 25 weeks, plus radiation therapy. This standard treatment and its risks are described in Attachments 1 and 2. The research part of the study is to see if there are things about the tumor cells that might tell us which subjects might have their disease return, or *relapse*, after the standard therapy.
2. Subjects with Stage III Wilms tumor who are found to have the LOH change will not stay on this study. They can enroll on another COG study, AREN0533, or they can discuss other treatment options with their doctor.

RESEARCH STUDY TESTS AND PROCEDURES

No additional tests or procedures will be done because you are on this study. Standard tests and procedures are described in Attachment #1.

HOW LONG IS THE STUDY?

Subjects in this clinical trial are expected to get treatment on this study over a period of about 25 weeks if on Regimen DD-4A. After treatment, subjects will have follow-up examinations and medical tests for about eight years. COG would like to continue to find out about your health for about eight years after you enter the study. Keeping in touch with you and checking on how your health is every year for a while after you complete treatment helps us understand the long-term effects of the study.

Your doctor or the researcher may decide to take you off this protocol therapy under the following circumstances:

- if he/she believes that it is in your best interest
- if the disease grows larger during treatment on this study
- if you have side effects from the treatment that are considered too severe
- if new information becomes available that shows that another treatment would be better for you

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY AND HOW ARE THE RISKS DIFFERENT FROM TREATMENT?

Treatment Risks

All people who get cancer treatment are at risk of having side effects. In addition to killing tumor cells, cancer chemotherapy can damage normal tissue and produce side effects. Side effects are usually reversible when the medication is stopped but occasionally persist and cause serious complications. A person can die from these and other complications. **For very young subjects, risks from the drugs may be worse, or may not appear until later in life.**

Common side effects include nausea, vomiting, hair loss, mucositis and fatigue. Drugs may be given to prevent or decrease nausea and vomiting. Hair loss is usually temporary but on very rare occasions it may be permanent. There is also the possibility that a second cancer may develop years later as a result of the chemotherapy. The risks of the individual drugs given as standard treatment and risks of radiation therapy are listed on the tables in **Attachment #2**. Side effects can be increased when chemotherapy drugs are combined.

The most common serious side effect from cancer treatment is lowering of the number of blood cells resulting in anemia, increased chance of infection, and bleeding tendency. Low blood counts are described in your Family Handbook for Children with Cancer. You will be taught more about caring for your child when his or her blood counts are low.

There is a risk that the treatment plan will not get rid of the cancer or that the cancer can go away after the treatment and then come back at a later date.

Reproductive risks

Women should not become pregnant and men should not father a baby while on this study because the drug(s) in this study can be bad for an unborn baby. If you or your partner can get pregnant, it is important for you to use birth control or not have sex while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some birth control methods might not be approved for use in this study. Women should not breastfeed a baby while on this study. Also check with your doctor about how long you should not breastfeed after you stop the study treatment(s).

Risks of Study

The addition of doxorubicin in Regimen DD-4A for Subjects with Stage I or II Wilms tumor who have the LOH change may cause more complications.

Risks and side effects related to doxorubicin include those which are:

Likely	Less Likely	Rare But Serious
<ul style="list-style-type: none"> • Nausea • Vomiting • Temporary hair loss • Pink or red color to urine, sweat, tears, saliva • Fewer white blood cells, red blood cells and platelets in the blood. <ul style="list-style-type: none"> ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily • Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function 	<ul style="list-style-type: none"> • Inflammation and/or sores in the mouth (and/or throat and /or esophagus, the tube that leads from the mouth to the stomach) that may make swallowing difficult and are painful (painful mouth sores) • Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid • Facial flushing • Fever/chills • Hives • High levels of uric acid in the blood which could damage the kidneys • Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed. • Damage to the skin if the medication leaks from a vein • Thickening and hardening of the veins through which the medication is given • Reddening reaction of the vein through which the drug is given. • Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage. • Tearing and inflammation of the eyes • Loss of appetite • Redness and burning at sites which have received radiation in the past • Diarrhea 	<ul style="list-style-type: none"> • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Ulceration of the lower intestinal tract • An irregular heart beat which can be life-threatening • Severe damage to the heart muscle which may lead to severe heart failure • A new cancer or leukemia resulting from this treatment.

The risk of heart damage may be greater in very young children than in older ones.

In addition to the risks described above, there may be unknown risks, or risks that we did not anticipate, associated with being in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We hope that you will get personal medical benefit from participation in this clinical trial, but we cannot be certain. You may benefit from the addition of doxorubicin to standard therapy if the additional therapy makes the tumor less likely to return.

We expect that the information learned from this study will benefit other patients in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- **Current standard therapy without being on this study**
- **Taking part in another clinical trial**

Please talk to your doctor about these and other options.

WHAT ABOUT PRIVACY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about this certificate is in Attachment #3 of this consent.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- **The Children's Oncology Group**
- **Representatives of the National Cancer Institute (NCI), Food and Drug Administration (FDA), and**
- **other U.S. and international governmental regulatory agencies involved in overseeing research**
- **The Institutional Review Board of this Hospital**
- **The Pediatric Central Institutional Review Board (CIRB) of the National Cancer Institute**

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. There are no plans for the study to pay for medical treatment. Please ask about any expected added costs or insurance problems. Staff will be able to assist you with this.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate

you in the event of injury. However by signing this form, you are not giving up any legal rights to seek to obtain compensation for injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

If you choose to enroll on this study, this institution will receive some money from the Children's Oncology Group to perform the research. There are no plans to pay you for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to be in this study. If you decide not to be in this study, you will not be penalized and you will not lose any benefits to which you are entitled. You will still receive medical care. You may stop being in the study at any time. If you stop being in the study, you will not be penalized and you will not lose any benefits to which you are entitled. Physicians and hospital personnel will still take care of you.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. A committee outside of COG closely monitors study reports and notifies institutions if changes must be made to the study. Members of COG meet twice a year to evaluate results of treatment and to plan new treatments.

During your follow-up visits after treatment, you may ask to be given a summary of the study results after they are written up. This may be several years after treatment for all people on the study is completed.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or if you have a research-related problem or if you think you have been injured in this study, you may contact Dr. XXXX or your doctor at ###-###-####.

If you have any questions about your rights as a research participant or any problems that you feel you cannot discuss with the investigators, you may call XXXX IRB Administrator at ###-###-####

If you have any questions or concerns that you feel you would like to discuss with someone who is not on the research team, you may also call the Patient Advocate at ###-###-####

WHERE CAN I GET MORE INFORMATION?

The *Family Handbook for Children with Cancer* has information about specific cancers, tests, treatment side effects and their management, adjusting to cancer, and resources. Your doctor can get you this Handbook, or you can get it at www.curesearch.org

If you are in the United States you may call the NCI's *Cancer Information Service* at 1-800-4-CANCER (1-800-422-6237)

Visit the *NCI's Web site* at <http://www.cancer.gov>

Visit the *COG Web site* at <http://www.curesearch.org>

Information about long term follow-up after cancer treatment can be found at <http://www.survivorshipguidelines.org/>

A description of this clinical trial will be available at: <http://www.ClinicalTrials.gov>, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

You will get a copy of this form. You may also ask for a copy of the protocol (full study plan).

SIGNATURE

I have been given a copy of all _____ [insert total number of pages] pages of this form. The form includes three (3) attachments.

I have reviewed the information and have had my questions answered.
I agree to take part in this study.

Participant _____ Date _____

Parent/Guardian _____ Date _____

Parent/Guardian _____ Date _____

Physician/PNP obtaining consent _____ Date _____
IRB# _____ IRB Approved: _____

Attachment #1
Treatment and Procedures Common to all Patients with Wilms Tumor

Central Line

For drugs to be given by vein, your doctor will likely recommend that you have a central venous line placed. A description of the types of central lines is in your Oncology Family Notebook.

Methods for Giving Drugs

Various methods will be used to give drugs to patients. The drugs on this study will be given using a needle or tubing inserted into a vein (**IV**).

Standard DD-4A Therapy:

<i>Drug</i>	<i>How the drug will be given</i>	<i>Days</i>	<i>Week</i>
Vincristine	IV over 1 minute*	On Day 1	1-10, 13, 16, 19, 22, 25
Dactinomycin	IV over 1-5 minutes	On Day 1	1, 7, 13, 19, 25
Doxorubicin	IV over 15-120 minutes	On Day 1	4, 10, 16, 22

* Vincristine can be given over one minute or using a minibag over several minutes by some institutions.

Radiation therapy is delivered during the first few days of the treatment schedule.

Standard tests and procedures

The following tests and procedures are part of regular cancer care and may be done even if you do not join the study:

- Frequent labs to monitor blood counts and blood chemistries
- Urine tests to measure how the kidneys are functioning
- Pregnancy test for females of childbearing age before treatment begins
- X-rays and scans to monitor the patient's response to treatment
- Tests to monitor heart and lung functioning

Standard tests and procedures that will be done to follow your progress after the study therapy is done are listed below:

What will be done:	How often:
History and Physical exam	Every three months for 3 years Every six months for the next two years then every two years [#]
Urinalysis	At three and six months after completion of treatment Every six months until 3 years Every year until 5 years then every two years [#]
Blood tests	Every 3 months for 1 year Every six months until 3 years Every year until 5 years.
Nuclear or urine test for kidney function	Every year for five years after completion of treatment
CT chest	Every 6 months for 3 years beginning 6 months after completion of treatment
Chest X-ray	Every 6 months for 5 years beginning 3 months after completion of treatment
CT or MRI abdomen/pelvis	Every 6 months for 3 years beginning 6 months after completion of treatment
Abdominal ultrasound	Every 6 months for 5 years beginning 3 months after completion of treatment
ECG/Echocardiogram*	At 2 years after completion of treatment

[#] Until we stop collecting medical information about you.

* If your doctor thinks you need these tests.

Attachment #2
Risks of Chemotherapy Drugs and Radiation Therapy

Risks and side effects related to dactinomycin include those which are:

Likely	Less Likely	Rare But Serious
<ul style="list-style-type: none"> • Nausea • Vomiting • Temporary hair loss • Fewer white blood cells, red blood cells and platelets in the blood. <ul style="list-style-type: none"> ○ A low number of red blood cells can make you feel tired and weak ○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets causes you to bruise and bleed more easily 	<ul style="list-style-type: none"> • Inflammation and/or ulceration (rarely) of the lips, the mouth, throat, esophagus, intestines or rectum • Fever • Diarrhea and/or abdominal pain • Damage to the skin if the medication leaks from a vein • Elevation in the blood of certain enzymes found in the liver which could indicate liver irritation or damage • Loss of appetite • Redness, burning or a darkening of the skin at sites which have received radiation in the past • A feeling of extreme tiredness, weakness or not feeling well • Muscle aches and pains • Acne or other types of skin bumps • Lower levels of calcium in the blood • A slowing of normal growth 	<ul style="list-style-type: none"> • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Inflammation or damage to the liver which can be severe and life-threatening and which may lead to an enlarged liver and spleen, bleeding from the veins in the esophagus (the passage that leads from the throat to the stomach), a yellow appearing skin, and fluid collection in the abdomen which makes it look larger. • Inflammation of the lungs which could lead to chest pain and discomfort • A new cancer or leukemia resulting from this treatment

Risks and side effects related to vincristine include those which are:

Likely	Less Likely	Rare But Serious
<ul style="list-style-type: none"> • Hair loss • Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes • Constipation 	<ul style="list-style-type: none"> • Jaw pain • Headache • Muscle weakness • Pain and bloating in your abdomen • Numbness and tingling • Wrist or foot drop • Drooping eyelids • Double vision, difficulty seeing at night • Hoarseness of your voice • Difficulty sweating • Abnormal walk with foot slapping • Difficulty with urination or increase desire to urinate • Dizziness and low blood pressure when you stand • Abnormal hormone function which may lower the level of salt in the blood • A mild drop in white blood cells, red blood cells and platelets in the blood <ul style="list-style-type: none"> ○ a low number of red blood cells can make you feel tired and weak ○ a low number of white blood cells can make it easier to get infections ○ a low number of platelets causes you to bruise and bleed more easily 	<ul style="list-style-type: none"> • Complete stoppage of your intestinal activity which can result in intestinal blockage • If the drug leaks out of the vein when being administered it will cause damage to nearby tissue • Seizures • Vocal cord paralysis • Difficulty breathing • Inability to walk • Decreased ability to hear clearly • Damage to the nerve to the eye (optic nerve) leading to decreased vision and possible blindness • In combination with other chemotherapy drugs: damage to the liver which can lead to inflammation and/or scarring which could lead to a yellow appearing skin, and fluid collection in the abdomen (belly) which makes it look larger

Radiation Therapy risks:

The radiation oncologist will discuss in detail the risks involved with radiation therapy when you sign the consent for the radiation therapy. The radiation oncologist will show you which part of the body will receive radiation therapy. In general, the side effects of radiation therapy are limited to the site of treatment and may include: temporary hair loss, nausea, vomiting, diarrhea, redness or dryness of the skin, low blood counts, mouth sores and/or injury to tissues or organs that may be included in the treatment field. Sterility may be associated with ovarian or testicular irradiation.

Potential late effects of radiation therapy may include problems with soft tissue or bone growth, vision problems, changes in endocrine function (low hormone levels), learning disabilities or brain injury, and increased risk for developing another cancer. These late effects depend on which part of the body receives radiation therapy, the age of the patient, and the drugs and surgery given at the same time as part of the therapy.

Attachment #3
Information about the Certificate of Confidentiality

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.