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**CHILDREN'S ONCOLOGY GROUP**

**AHOD0031**

# A Phase III Groupwide Study of Dose-Intensive Response-Based Chemotherapy and Radiation Therapy for Children and Adolescents with Newly Diagnosed Intermediate Risk Hodgkin Disease

**An Intergroup Study for Participation by COG, the Dutch Childhood Oncology Group**
- **SKION (Stichting Kinderoncologie Nederland), and**
- **ISPHO (the Israeli Society of Pediatric Hematology and Oncology)**



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## ABSTRACT

Cure rates for pediatric Hodgkin disease remain among the highest in pediatric oncology. However, cure often comes with a significant cost in the form of delayed effects of therapy. This protocol will evaluate a dose intensive regimen ABVE-PC in the treatment of intermediate risk Hodgkin disease. This protocol will combine dose intensity with response-based augmentation or reduction in therapy to 1) improve outcome for all intermediate risk pediatric patients with Hodgkin disease and 2) decrease the risk for delayed effects of treatment. The standard arm for this protocol will be 4 cycles of ABVE-PC plus consolidative involved field radiation therapy. Slow early responders will be randomized to either the standard arm, or the augmented therapy arm, which will add 2 additional cycles of different chemotherapy (DECA) to the standard arm. Rapid early responders who then go on to a complete response following 4 cycles of chemotherapy will be randomized to the standard arm, or the reduced therapy arm, where consolidative radiation therapy will be omitted.

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## 1.0 SPECIFIC AIMS AND HYPOTHESES

### 1.1 Aims

1.11
To compare response-based therapy to standard therapy for intermediate risk Hodgkin disease.

1.12
To determine whether involved field radiation therapy (IFRT) can be eliminated based upon early and complete response to multiagent chemotherapy.

1.13
To determine whether the addition of an additional two cycles of chemotherapy (DECA) can improve outcome in those with a slow early response to standard chemotherapy.

1.14
To prospectively collect information on the individual prognostic significance of the following presenting factors: erythrocyte sedimentation rate, circulating levels of IL-10, each of the "B" symptoms - fever, night sweats, weight loss, nodal aggregate > 6 cm, large mediastinal mass > 1/3 thoracic diameter and number of involved nodal sites, histology, albumin, blood counts, sex and age.

1.15
To study the reliability and utility of [$^{18}$F] –Fluorodeoxyglucose (FDG) Imaging (PET scans) as an imaging modality in Hodgkin disease.

1.16
To determine the frequency and severity of late effects of therapy including thyroid dysfunction, infertility, cardiotoxicity, pulmonary toxicity and second malignant neoplasms.

1.17
To serve as the therapeutic companion to biology studies in Hodgkin disease and correlate those results with response to therapy, event free-survival and overall survival.

### 1.2 Hypotheses

1.21
For rapid early responders (RER) in a treatment regimen which adapts treatment to response as defined below, response-based therapy will provide a superior or an equivalent outcome.

1.21a
Involved field radiation therapy can be omitted in selected pediatric patients with intermediate risk Hodgkin disease (those with rapid early response after 2 cycles of ABVE-PC followed by a complete response following an additional 2 cycles).

1.22
For slow early responders (SER) in a treatment regimen which adapts treatment to response as defined below, response-based therapy will provide a superior or an equivalent outcome.

1.22a
Augmentation of ABVE-PC chemotherapy by the addition of 2 cycles of non-cross reacting DECA chemotherapy will improve outcome in pediatric patients with intermediate risk Hodgkin disease who have an initial slow early response to 2 cycles of ABVE-PC.

1.23
Analysis of prognostic factors may provide additional information regarding risk stratification for patients with pediatric Hodgkin disease who may successfully be treated with response-based therapy.

1.24
[$^{18}$F]–Fluorodeoxyglucose (FDG) imaging (PET scans) will have good sensitivity, specificity, and positive and negative predictive values for detection of Hodgkin disease and assessment of residual disease following therapy.

1.25
Long-term toxicities of therapy can be decreased without compromising response rate and overall disease free survival.

1.26
Understanding the biologic mechanisms of Hodgkin disease and host factors associated with response and toxicity will facilitate the development of more efficacious and less toxic approaches to Hodgkin disease therapy.

## 2.0 OVERVIEW OF STUDY DESIGN

### 2.1 Protocol Abstract

This study is intended to evaluate response-based therapy for patients with intermediate risk Hodgkin disease. Therapy may be reduced or augmented based upon early response to chemotherapy.

All patients will receive 2 cycles of ABVE-PC three weeks apart followed by a re-evaluation of disease.

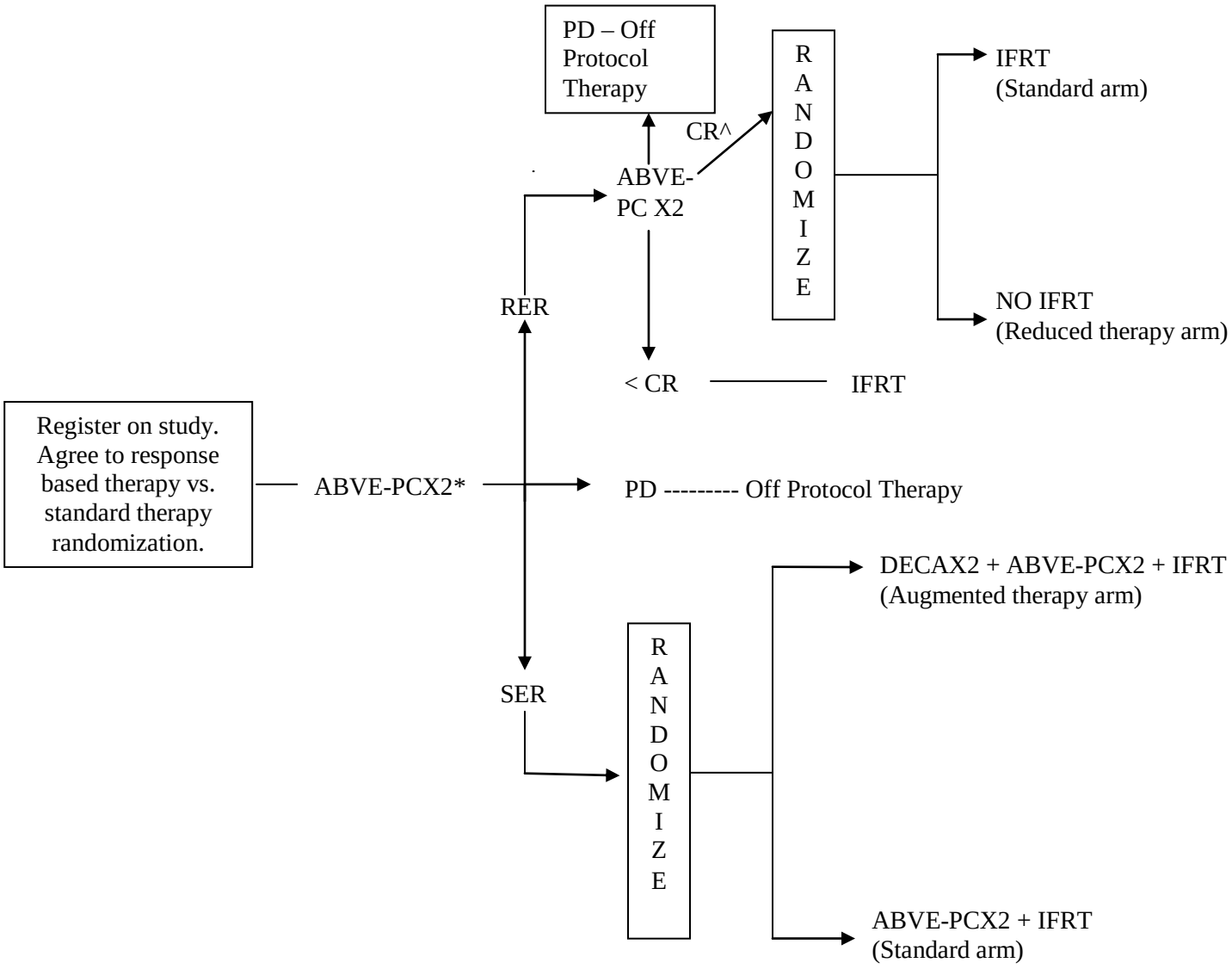
Those with a rapid early response will receive an additional 2 cycles of ABVE-PC followed by another re-evaluation of disease. Rapid early responders, who have sustained a complete response following a total of 4 cycles of ABVE-PC chemotherapy, will be randomized to omit (reduced therapy arm) or receive consolidative low dose involved field radiation therapy (IFRT) (standard therapy arm). Those with less than a complete response will receive IFRT.

Patients with a slow early response to 2 cycles of ABVE-PC will be randomized to receive 2 additional cycles of ABVE-PC (standard therapy arm) alone versus 2 additional cycles of ABVE-PC preceded by 2 cycles of DECA (augmented therapy arm). All patients who are slow early responders will receive consolidative low dose IFRT.

Patients with less than a complete response after consolidative radiation therapy or those with progressive disease at any time will be treated at the discretion of the treating physician after consultation with the study chair.

At the time of study entry patients must agree to the possible randomizations inherent in this response based therapeutic study.

## 2.2 Experimental Design Schema




*At the end of the first 2 cycles of ABVE-PC, Call-back #1 should take place for all patients in order to determine RER or SER status. Central review by QARC is required for this assessment.

^At the end of 4 cycles of ABVE-PC for RER patients, Call-back #2 should take place in order to confirm CR status and proceed with RT randomization. Central review by QARC is required for this assessment.

## 3.0 BACKGROUND AND RATIONALE

### 3.1 Introduction

Cure rates for pediatric Hodgkin disease remain among the highest in pediatric oncology. However, cure often comes with a significant cost in the form of delayed effects of therapy, including an elevated risk for second malignant neoplasms, cardiotoxicity, pulmonary toxicity, gonadal and nongonadal endocrine dysfunction. Improvement of therapeutic outcome combined with reduction in the incidence of delayed effects of treatment has been slow for intermediate risk patients over the most recent pediatric cooperative group studies.

This is the first of several planned protocols for initial therapeutics for Hodgkin disease and addresses the following overall goals: 1) to evaluate response-based therapy; 2) to evaluate dose-intensive therapy; 3) to develop therapeutic approaches directed towards improvement of outcome combined with reduction of long-term complications of therapy and 4) to link enrollment on therapeutic studies with enrollment on biological studies that are being developed by subcommittees within the COG Hodgkin Disease committee.

This protocol will combine dose intensity with response-based augmentation or reduction in therapy to 1) improve outcome for all intermediate risk pediatric patients with Hodgkin disease and 2) decrease the risk for delayed effects of treatment.

### 3.2 Clinical Trials to Date

Since the initial use of MOPP in the 1960's, marked improvement in cure rate has taken place in pediatric Hodgkin disease[1] Donaldson and colleagues at Stanford introduced the concept of combined modality therapy for pediatric patients using the MOPP backbone and low-dose radiation therapy.[2,3] Subsequent therapies have built upon the MOPP backbone. ABVD was added as an alternative effective regimen in an attempt to improve survival and decrease long-term effects of treatment. Published complete remission rates with MOPP, MOPP/ABVD and ABVD range from 69% to 92%, with the results for each regimen varying considerably from study to study.[4] Event-free survival for intermediate and high risk Hodgkin disease appears fairly stable over the past decade. In CCG 521, patients were randomized between 12 cycles of alternating MOPP/AVBD versus 6 cycles of AVBD + low dose regional chemotherapy. Event-free survival was only 77% for Stage III and IV patients.[5] The German cooperative groups have built upon COPP chemotherapy in both pediatric and adult Hodgkin disease. The DAL-HD-90 study uses OEPA/COPP for males and OPPA/COPP for females, both followed by IFRT. EFS for Stages II, III, and IV are 92, 86 and 90% respectively.[6] In adults, a dose intensified rearranged form of COPP/ABV with etoposide added, BEACOPP was compared with COPP/ABV in patients with Stage IIB, III and IV. EFS was 84% vs. 75%.[7] A dose intensive therapy developed at Stanford using MOPP/ABVE given over 12 weeks followed by IFRT offers an EFS of 89% for stage IIB bulk, III and IV patients.[8] However, these dose-intensified studies are accompanied by radiation therapy and thus are associated with increased potential for delayed effects of treatment from combined alkylating agents and radiation therapy.

In an attempt to decrease alkylator therapy and potential cardiotoxicity, the Pediatric Oncology Group (POG) developed a series of studies built upon the ABVD backbone, substituting dacarbazine with etoposide. The use of vincristine instead of vinblastine allows for escalation of doxorubicin and VP-16. POG 9226 piloted therapy with 4 cycles of DBVE followed by low dose IFRT in patients with Stages I, IIA and IIIA. 5-year EFS was 89%. POG 9426 evaluates the same chemotherapy in a non-randomized response-based manner. Those with a complete response after 2 cycles receive consolidative IFRT and receive no further chemotherapy. In POG 9425 (for patients with advanced stage disease) prednisone and cyclophosphamide are included. Response is assessed after 3 cycles and those with complete response (CR) do not receive the additional 2 cycles of chemotherapy. All patients receive consolidative IFRT. Both studies evaluate the efficacy of dexrazoxane in reducing cardiac and pulmonary toxicity.

With the goal of continued excellent long-term survival and decreasing long-term effects of treatment, POG and the Children's Cancer Group (CCG) conducted trials to evaluate elimination of radiation therapy. POG 8725 compared 8 cycles of MOPP/AVBD with and without IFRT in Stage IIB, III and IV patients. There was no significant benefit for radiation therapy.[9] The study used a large amount of chemotherapy which is associated with potential significant long-term adverse outcomes including gonadal toxicity, cardiac toxicity and secondary leukemia. Response post 3 cycles was a strong prognostic factor, with a 94% EFS in the rapid early responders as opposed to a 78% EFS in those who did not respond quickly.[9] There was no change in therapy for slow early responders and the comparison was made retrospectively. CCG 5942 studied the elimination of radiation therapy in a randomized fashion in all patients who had a complete response following chemotherapy. Patients were treated with 4 cycles of COPP/ABV, 6 cycles of COPP/ABV or 2 cycles each of COPP/ABV, Ara-C/VP16, and CHOP, depending on stage of disease and presence of bulk disease. EFS for all Stage II, III and IV patients was 84.4%, 76% and 81% at 4 years, respectively. In all groups the difference in EFS post randomization was highly significant and overall EFS was 91% for the group who received IFRT and 86% for those who did not receive IFRT. This benefit is likely to be small compared to the morbidity in a group of patients with a high likelihood of cure, but large in comparison to morbidity in patients with a lower likelihood of cure. The overall survival was 99% in both groups. Presence of bulk disease, B symptoms and elevated sedimentation rate were poor prognostic factors. (Sposto, personal communication). Early response to therapy was not evaluated in the CCG study. Comparison of these studies demonstrates several important points: 1) The choice of chemotherapy (agents, cumulative dose, intensity) must be carefully considered if omission of radiation therapy is considered. Excessive chemotherapy may obviate the need for radiation therapy; 2) Early rapid response may be an important positive prognostic factor to consider elimination or reduction of RT; 3) Patient subgroups for whom radiation therapy may be safely omitted has not yet been discerned with the regimens that have been employed to date 4) Adverse prognostic factors should be considered in developing risk strata and determination of response.

This study builds upon previous POG and CCG studies that evaluated omission of RT. This chemotherapy backbone (ABVE-PC) is a logical extension to POG 9425 and 9426, which use DBVE+PC as the chemotherapy backbone. While number of cycles in those studies is based on early response, no other response based questions are posed nor is there randomization of the response-based approach. Use of a similar chemotherapy backbone will allow us to have some degree of common treatment across existing and new studies. It will also allow us to compare the modifications to this backbone that are included in the new generation of studies.

### 3.3 **Prognostic Value of Rapid Early Response**

Extrapolating data from acute lymphoblastic leukemia, there appears to be a rationale to tailor therapy based upon a rapid early response.[10] Response-based therapy has not yet been studied in pediatric Hodgkin disease in a randomized manner. POG 8725 collected data on early response and reported those with a CR after 3 cycles to have a much-improved outcome compared with slower responders (94% vs. 78% 5 year EFS).[9] POG 9425 and 9426 have reduced chemotherapy for those who sustain an early complete response. The French Society of Pediatric Oncology recently published data on the response-adapted therapy. The dose of radiotherapy and/or additional chemotherapy was given based upon early response to their chemotherapy backbone. While EFS is this study was excellent, patients received 2000 - 4000 cGy of radiotherapy, both involved and extended field, based on response and presenting factors.[11] CCG 59704 stratifies chemotherapy in a gender-specific fashion based on rapid complete response. None of these studies randomize between response-based and non response-based therapy. Therefore, tailoring therapy based on early response is an important and unanswered question in pediatric Hodgkin disease.

### 3.4 Prognostic Markers

In CCG 5942, univariate analysis revealed the following to be of prognostic significance: stage of disease, erythrocyte sedimentation rate, B symptoms, and presence of nodal aggregate >10 cm and/or large mediastinal mass. In stratified Cox analysis large nodal aggregate, and elevated erythrocyte sedimentation rate and B symptoms remained statistically significant risk factors for inferior outcome. (Sposto personal communication) With respect to B symptoms, fevers and weight loss may be more important prognostically than night sweats in patients with Stage IB and IIB disease.[12] Studies in adults suggest that high pre-treatment circulating levels of IL-10 are associated with a poor prognosis irrespective of other common prognostic variables.[13-15] These factors have been taken into consideration for the definitions of eligibility for the present study. In addition, there will be evaluation of both pretreatment erythrocyte sedimentation rate and circulating levels of IL-10 as prognostic factors. Among adult groups a consortium has developed a prognostic score for advanced Hodgkin disease, which is widely utilized. This model includes serum albumin, hemoglobin, male sex, age, stage IV disease, white blood cell count $\geq$ 15,000/mm3 and lymphocyte count < 600/mm3 or < 8% of the total white blood cell count.[16] Clearly this would require adaptation for use in pediatrics. Based on the MDH90 study, the French Pediatric Oncology Group developed a prognostic scoring system that was fitted retrospectively to the results of that study. The system includes hemoglobin, mediastinal mass and nodular sclerosing disease.[11]

### 3.5 Dose Escalation

Intensity of treatment with delivery of higher doses of chemotherapy over a shorter period of time to improve outcome is a recurring theme in pediatric oncology. Van Rijswijk showed loss of dose intensity of nitrogen mustard and vincristine resulted in decreased survival.[17] Carde similarly found that the rates of drug delivery during the first three cycles of MOPP are important in achieving maximum complete response rates especially for patients with B-symptoms.[18] Administration of chemotherapy agents for HD in a more intensive manner may therefore improve long-term outcome. This approach is being evaluated in 3 POG HD studies, 9226, 9425 and 9426, and in CCG 59704. This approach has been used successfully in Stanford V [8] and BEACOPP,[7] both of which show event-free survival in the 89% range. Dose intensity and cumulative dose of various regimens are shown in Tables 3.51 & 3.52. This regimen offers the potential benefits of dose intensity without increased cumulative doses that may result in increased regimen-related and long-term toxicity.

**TABLE 3.51: DOSE INTENSITY OF CHEMOTHERAPIES (mg/m²/week)**

| | BEACOPP | BEACOPP E | MOPP/AVBD | COPP/AVB | DBVE | DBVE-PC | AVBE/PC |
|---|---|---|---|---|---|---|---|
| Dox | 8.3 | 11.7 | 6.3 | 6.3 | 12.5 | 20 | 16.7 |
| Bleo | 3.3 | 3.3 | 2.5 | 2.5 | 5 | 6.70 | 5 |
| VCR | .46 | .46 | .35 | .35 | .7 | .93 | .93 |
| VP16 | 100 | 200 | 0 | 0 | 125 | 125 | 125 |
| PDN | 187 | 187 | 70 | 70 | 0 | 133 | 93 |
| CPM | 217 | 417 | (NH2 – 1.5) | 163 | 0 | 267 | 267 |
| PRO | 233 | 233 | 175 | 175 | 0 | 0 | 0 |
| VBL | 0 | 0 | 1.5 | 1.5 | 0 | 0 | 0 |
| DTIC | 0 | 0 | 94 | 0 | 0 | 0 | 0 |

## TABLE 3.52: COMPARATIVE DOSES OF CHEMOTHERAPY PROTOCOLS

| Drug | BEACOPP4 +ABVD2 (Males) CCG59704 | BEACOPP4 +COPP/ABV4 (Females) CCG59704 | BEACOPP 8 | COPP/ABV4 CCG 5942 | COPP/ABV6 CCG 5942 | (ARA/VP COPP/ABV CHOP)2 CCG 5942 | MOPP/ ABVD6 CCG 521 | ABVD6 CCG 521 | DBVE POG 9426 dept on course # | DBVE-PC POG 9425 dept on course # | OEPA/ COPPX2 | OEPA/ COPPX4 | ABVE-PC4 | ABVE-PC4 + DECA2 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dox** | 240 | 280 | 280 | 140 | 210 | 220 | 300 | 300 | 100/200 | 180/300 | 160 | 160 | 200 | 200 |
| **Ara-C (g)** | 0 | 0 | 0 | 0 | 0 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 |
| **Bleo(U)** | 80 | 80 | 80 | 40 | 60 | 20 | 120 | 120 | 40/80 | 45/60 | 0 | 0 | 75 | 75 |
| **CDDP** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 90 |
| **CPM** | 5000 | 7400 | 10000 | 2400 | 3600 | 6000 | 0 | 0 | 0 | 2400/4000 | 1000 | 2000 | 3200 | 3200 |
| **DTIC** | 1500 | 0 | 0 | 0 | 0 | 0 | 4500 | 4500 | 0 | 0 | 0 | 0 | 0 | 0 |
| **DXM** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 40 |
| **VP16** | 2400 | 2400 | 4800 | 0 | 0 | 1600 | 0 | 0 | 1000/2000 | 1125/1875 | 1000 | 1000 | 1500 | 1900 |
| **MePDN** | 0 | 0 | 0 | 0 | 0 | 2000 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **NH2** | 0 | 0 | 0 | 0 | 0 | 0 | 72 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **PDN** | 2240 | 4640 | 4480 | 2240 | 3360 | 1600 | 3360 | 0 | 0 | 1200/2000 | 3000 | 4200 | 1400 | 1400 |
| **PROC** | 2800 | 5600 | 5600 | 2800 | 4200 | 1400 | 8400 | 0 | 0 | 0 | 3000 | 6000 | 0 | 0 |
| **VBL** | 24 | 24 | 0 | 24 | 36 | 14.8 | 72 | 72 | 0 | 0 | 0 | 0 | 0 | 0 |
| **VCR** | 8 | 13.6 | 16 | 5.6 | 8.4 | 2.8 | 16.8 | 0 | 6/12 | 8.4/14 | 15 | 21 | 14 | 14 |

### 3.6 Prevention of Late Effects

Alkylating agents and radiation have been the principal therapies responsible for the excellent survival rates in Hodgkin disease; they also share the etiologic spotlight for late toxicities. Subsequent malignant neoplasms (SMNs) including leukemia, thyroid cancer, breast cancer, soft tissue sarcomas, and other solid tumors are reported in excess in survivors of pediatric Hodgkin disease. The dose and type, and perhaps schedule of chemotherapy are important in assessing risk. The risk of breast cancer following HD is a significant factor in seeking to reduce or eliminate RT in females. However the full spectrum of SMNs must be considered in designing therapy to reduce SMNs. With lower involved field radiation therapy females may not be at the same increased risk of breast cancer as they would be with a higher dose and a more extended field. Survivors of HD disease are also at risk for other cancers that appear associated with radiation including sarcomas, melanoma, lung, and gastrointestinal cancers. While breast cancer incidence is rising rapidly and is seen to date only in female survivors, the gender effect on both relative risk and absolute risk for SMNs varies. Independent of gender, younger age at diagnosis conveys a significant relative risk for all radiation therapy-associated cancers, as does relapsed disease.[19-27]

Thyroid dysfunction (hypothyroidism, hyperthyroidism, goiter, nodules, cancer) is a common delayed effect of radiation therapy for Hodgkin disease.[28,29] The relative risk for thyroid cancer is not consistently higher for males or females across studies.[20,22,24,25] Radiation therapy in the pediatric population can also result in soft tissue hypoplasia and diminution of bone growth, effects that may be decreased or eliminated by reduced dose or fields and by omission of radiation therapy.[30]

For males, there is a clear association between alkylating agent exposure and gonadal toxicity. The response is dose specific and worsens with multiple alkylators. In a study of sarcoma patients who received cyclophosphamide and dacarbazine without procarbazine, 70% had recovery of sperm function within 5 years if they received < 7.5gm/m² cyclophosphamide, whereas recovery was seen only in 10% who received higher than this cumulative dose.[31] Pryzant found a similar association with a CHOP-BLEO regimen for NHL, where sperm recovery was seen in 83% of patients who received < 9.5gm/m² and only 47% in those with higher cumulative doses.[32] In a recent study of male survivors of childhood cancer, patients treated with 5 gm/m² or less of cyclophosphamide had normozoospermia.[33] Addition of other alkylating agents such as procarbazine results in permanent azoospermia in > 90% of patients after much lower cumulative doses of cyclophosphamide (4.8 g/m²).[34,35] Bokemeyer compared male gonadal dysfunction in patients treated with equal doses of cyclophosphamide for NHL and HD. The HD survivors, who had received a mean cumulative procarbazine dose of 13.3 g/m² had significantly more gonadal toxicity.[36] Several studies have shown that the addition of 2 - 6 cycles of COPP to either OPPA or OEPA markedly affect gonadal dysfunction.[37,38] Use of procarbazine without cyclophosphamide can also lead to gonadal dysfunction. A study of 46 males ages 8 - 15 years treated with chlorambucil, vinblastine, procarbazine and prednisone reported significant germinal epithelial damage in 89% and Leydig cell dysfunction in 24%.[39] Reduction of alkylating agent therapy in multiagent protocols has resulted in reduction in testicular dysfunction.[6,40,41] Elimination of all alkylating agents has resulted in the preservation of gonadal function in 92% of male patients.[42]

For females, risk of menstrual irregularity, ovarian failure, and infertility increase with age of treatment.[43-45] Amenorrhea and ovarian failure occur more commonly in adult women treated with cyclophosphamide than in adolescents, with prepubertal females tolerating cumulative doses as high as 25 gm/m².[46-48] In adult rat females cyclophosphamide is associated with a dose related depletion of antral follicles, decreased follicular diameter, and decreased serum estradiol.[49] Ovaries of human adult females treated with cyclophosphamide show an absence of theca cells and ova.[50] While adult females are most susceptible to the gonadal effects of chemotherapy, a decrease in the number of ovarian follicles has been documented in prepubertal girls treated with alkylating agent chemotherapy.[45] Adolescent females often recover gonadal function after completion of therapy, but are at risk for premature menopause. Two large studies have shown elevated relative risks for infertility and early menopause in female survivors of

childhood cancer. Byrne and colleagues found a relative risk of 9.2 for early menopause (ages 21-30 years) in postpubertal females treated with alkylating agents and an overall fertility deficit of 7% as compared with siblings.[51] Chiarelli found a pregnancy failure rate of 15.5% and a relative risk of infertility of 4.9 associated with alkylating agent use.[52] While cyclophosphamide appears less gonadal toxic than mechlorethamine, it remains unclear whether this will result in decreased risk of premature menopause long term.

The effect of pelvic irradiation if gonads are in the treatment field in both genders is again dose dependent with effects differing by dose delivered to the gonad.[53] It appears to be additive to the effects of chemotherapy.[32,51,52]

Delayed cardiac effects may occur from either anthracyclines and/or from the effects of irradiation. Cardiomyopathy risk from anthracyclines may be increased in females, with higher cumulative doses and younger age at diagnosis, and with longer follow-up time. Females appear to have increased risk for both early and late cardiotoxicity of anthracyclines.[54-64] However, the risk in males in not insignificant. As patients get further out from treatment, worsening of cardiac function is noted.[59] The gender effect may not be preserved over time. Doxorubicin-related cardiac abnormalities are reported with increased frequency in females, treated with higher cumulative dose and at a younger age. Although the dose of doxorubicin used in Hodgkin disease is usually below the threshold value (300 mg/m²,) children may be more sensitive than adults to the cardiotoxic effects of doxorubicin, especially in combination with radiation therapy.[60,61] Radiation to the chest in higher doses than currently used in Hodgkin disease can result in coronary artery disease.[62-64] Evolving data reveals that the risk of coronary artery disease from thoracic radiation may be greater in males (Wolden, Personal Communication).

Bleomycin has been shown to cause pulmonary fibrosis with a decrease in carbon monoxide diffusing capacity, in a dose-dependent manner.[65]

This chemotherapeutic regimen offers doses and types of alkylators that have not been associated with high rates of second cancers or gonadal toxicity. The long-term impact of using etoposide with respect to second leukemia risk remains unclear, but with respect to cumulative dose appears safe.[66] Avoidance of radiation therapy may result in fewer second solid tumors and avoidance of cardiopulmonary dysfunction and thyroid disease. While the spectrum of late effects differ somewhat by gender, there is benefit to be gained by both males and females if alkylator doses can be reduced and radiation therapy can be eliminated safely without compromising disease free survival.

### 3.7 Choice of Additional Chemotherapy for Slow Early Responders

A combination of dexamethasone, etoposide, cisplatin and cytarabine (DECA) will be studied in slow early responders to assess whether outcome can be improved for this group of patients. Prednisone has lympholytic and anti-inflammatory effects. Dexamethasone has been used successfully in Hodgkin and non-Hodgkin lymphoma relapse protocols.[67,68] In CCG 5912 Dexamethasone was combined with other agents in the DECAL chemotherapy regimen that resulted in 40% CR and 72% CR/PR in 29 children with Hodgkin disease.[68] Cisplatin, cytarabine and etoposide were also used in the POG APE chemotherapy salvage protocol. Complete remissions were achieved in patients with disease relapse following MOPP/COPP/AVBD therapy and without remission following other salvage therapies. [69] This regimen includes cisplatin and cytarabine both of which have been used in several relapse protocols, both separately and together.[67,68,70-72] These agents were also utilized in upfront therapy for advanced stage disease in the POG study of APPE/OPPA. For 74 evaluable patients, CR was obtained in 89% and 2-year EFS was 82.1%.[73] Dose intensity was similar to DECA, but the schedule of administration was more cumbersome. Cytarabine was also part of the therapy for Stage IV patients in CCG 5942, for whom there was an 81% 4-year EFS. (Sposto, Personal Communication) DECA proposed in this study is a logical extension to these studies, utilizing these agents upfront in slow early responders.

### 3.8 Imaging Response Criteria and Lesion Evaluation

Response criteria were adapted with some modification from the criteria from the Cotswolds Meeting, the International Workshop to Standardize Response Criteria for Non-Hodgkin Lymphomas, RECIST criteria and prior newly diagnosed Hodgkin disease protocols, including CCG 5942, CCG 59704, POG 9425, and POG 9426.[74-76]

Establishment of strict size criteria for presumptive lymphomatous nodal enlargement is complicated by a number of factors, including substantial size overlap between benign reactive lymphoid hyperplasia and malignant lymphadenopathy, interobserver measurement variability, obliquity of node orientation to the scan plane, multiplicity of criteria for size measurement (volumetric vs. bidimensional vs. unidimensional; short axis vs. long axis), variability of normal nodal size with body region and age, and the paucity of studies addressing normal node size in pediatric patients. Normal nodal size limit standards have been established in adults. However, for children and younger adolescents, there is less clarity. In younger children, application of adult size limits is confounded by the relatively high frequency of enlarged nodes from benign reactive hyperplasia. This process is particularly common in the cervical, axillary, mesenteric, and inguinal regions, and may be associated with nodes up to 1.5 - 2 cm in diameter. In other anatomic regions, including the supraclavicular, retroperitoneal, iliac, mediastinal, and hilar regions, normal nodes are typically less than 1 - 1.5 cm. Apart from nodal enlargement, features that suggest lymphomatous involvement include nodal clustering or matting, and nodal gallium or FDG avidity.

While acknowledging the limitations of nodal size assessment discussed above, the nodal size criterion used by prior newly diagnosed Hodgkin protocols (CCG 5942, POG 9425 and POG 9426, Stanford V) have been considered for simplicity and consistency. A contiguous nodal aggregate that measures > 6 cm in the longest transverse diameter is considered bulk disease, as is a mediastinal mass where tumor diameter is > 1/3 the thoracic diameter.

For visceral organs (such as liver, spleen, kidney) any focal mass lesion large enough to characterize is considered due to lymphomatous involvement unless the imaging characteristics indicate an alternative nature (e.g. cyst, hemangioma, abscess, etc.). Lesions too small to characterize are indeterminate unless follow-up studies allow characterization or tissue sampling is performed.

Measurable disease indicates the presence of at least one measurable lesion. Superficial lesions (e.g., palpable lymphadenopathy) may be measurable by clinical exam. A measurable lesion by CT is a lesion that can be accurately measured in two orthogonal dimensions. This typically involves lesions of at least 1 cm diameter, although the ability to establish a lesion as measurable by CT is influenced by multiple factors independent of actual lesion size, including the attenuation and enhancement pattern of the lesion relative to adjacent tissues, CT study technique and scanner performance, and observer diagnostic acumen and confidence.

All measurable lesions should be measured in the axial plane on CT. All measurable lesions up to a maximum of 6 lesions in total, representative of all involved organs, will be measured as target lesions at baseline and followed for response. Target lesions will be selected on the basis of size (i.e., largest lesions) and suitability for accurate repeated measurements by imaging or clinical exam. Lesions will be recorded with size expressed as the PPD (product of perpendicular diameters). The PPD is obtained by multiplying the longest diameter of the lesion by the maximal diameter perpendicular to the longest diameter. In a chain of lymph nodes, or in measuring the residual mediastinal mass at the end of therapy, care should be taken not to overestimate the PPD by measuring the cephalad-caudad diameter of the entire mass or lymph node chain when individual nodes can easily be discerned. The PPD serves as a surrogate measurement of area with dimensions of $cm^2$. The SPPD, or sum of the product of the

perpendicular diameters, is obtained by adding the products of the perpendicular diameters of measured lesions.

Non-measurable assessable lesions include permeative bone lesions, malignant ascites, malignant pleural/pericardial effusions, pulmonary or cutaneous lymphangitic spread, and lesions too small to accurately measure in two dimensions by CT. All non-target and non-measurable assessable lesions will be recorded at baseline and noted on follow-up.

## 4.0 STUDY ENROLLMENT AND PATIENT ELGIBILITY

### 4.1 Study Enrollment

#### 4.11 IRB Approval

Upon receipt of local IRB approval for a COG study, fax the officially signed IRB approval to the Group Operations Center (GOC) at: (626) 445-6715. The *COG IRB Approval Fax Cover Sheet* is required to be faxed with the official approval. A copy of this cover memo can be obtained from the protocol links area of the COG website. After this approval is recorded by GOC staff, the institution will have access to the eRDE enrollment screens.

#### 4.12 Patient Registration

Prior to study enrollment, all patients must have been registered via the eRDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

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. Please use this number as part of the labeling information on all banking and biology specimens sent to the Biopathology Center or a COG Reference Laboratory. If you have a question about a patient's BPC Number, please call the Biopathology Center at (800) 347-2486.

#### 4.13 Study Enrollment

Patients may be enrolled on the study 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 the online help in the Applications area of the COG website.

#### 4.14 Timing

Study enrollment must take place within five (5) calendar days of beginning protocol therapy. If enrollment takes place before starting therapy, the date protocol therapy is projected to start must be no later than ***five (5)*** calendar days after enrollment. Study enrollment must occur within 28 days of diagnosis and staging. If more than 28 days elapse before study enrollment, restaging of disease is required prior to study enrollment to confirm eligibility. Therefore any imaging study that is > 28 days old must be repeated. If the surgical diagnosis is > 28 days old, but all staging imaging studies are within 28 days, the patient can be enrolled on study.

All patients must agree to all possible randomizations dictated by this response based therapeutic study.

4.15 Bilingual Services

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

4.2 **Eligibility 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.**

4.21

Patients with newly diagnosed, pathologically confirmed Hodgkin disease (all histologies) are eligible for this protocol if they meet the following clinical stage guidelines:

- All Stage IB regardless of bulk disease
- All Stage IIB regardless of bulk disease
- Stage IA only with bulk disease
- Stage IIA only with bulk disease
- All Stage IAE, IIAE regardless of bulk disease
- All Stage IIIA, IIIAE, IIIAS, IIIAE+S regardless of bulk disease
- All Stage IVA, IVAE regardless of bulk disease

See Appendix I for definitions of clinical staging, E criteria, B symptoms and bulk disease.

4.22 Clinical Staging

Staging on this study will be determined by the clinical stage. Patients who have surgical staging (by laparotomy) alone are ineligible for entry on this protocol. Surgically staged patients may be entered on this study if they also have pre-surgical staging that meets the above criteria. Surgical staging is strongly discouraged.

4.23 Age

Ages 0 - 21 years inclusive.

4.24 Organ Function Requirements

4.241 Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 $m^2$ or
- A serum creatinine based on age/gender as follows:

| **Age** | **Maximum Serum Creatinine (mg/dL)** | |
|---|---|---|
| | **Male** | **Female** |
| 1 month to < 6 months | 0.4 | 0.4 |
| 6 months to < 1 year | 0.5 | 0.5 |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.242 Adequate liver function defined as:
- Total bilirubin ≤ 1.5 x normal, and
- SGOT (AST) or SGPT (ALT) < 2.5 x normal.

4.243 Adequate cardiac function defined as:
- Shortening fraction of ≥ 27% by echocardiogram, or if echocardiogram not feasible, ejection fraction of ≥ 50% by radionuclide angiogram (MUGA), unless due to large mediastinal mass from HD. Study chair approval required for entry onto protocol with shortening fraction < 27% or ejection fraction < 50%.
- No pathologic prolongation of QTc interval on 12-lead ECG

4.244 Adequate pulmonary function defined as:
- FEV1/FVC > 60% by pulmonary function test, unless due to large mediastinal mass from HD. Study chair approval required for entry onto protocol with FEV1/FVC≤ 60%
- For children who cannot adequately perform PFTs, no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94%. PFTs should not be attempted for children under the age of 7 years.

Patients with other pre-existing cardiac or pulmonary abnormalities require Study Chair approval prior to being placed on therapy.

4.245 Women who are pregnant or breast-feeding will not be eligible.

4.25 Previous therapies

Patients may not have received any previous chemotherapy, biological modifiers such as monoclonal antibody therapy or radiation therapy. Patients may not have received corticosteroids within 28 days of enrollment on this protocol, except as specified in Section 5.1 for emergent treatment for respiratory distress or spinal cord compression, or for treatment of contrast agent allergy required for CT scan.

4.26 Venous access

Adequate venous access is required. An infusaport (portacath) is recommended, but not required.

4.27 Informed Consent

The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent to become a study subject has been obtained, in accordance with institutional policies approved by the U.S. Department of Health and Human Services.

4.28 Protocol Approval

Approval for the use of this treatment protocol by the individual institution's Human Rights Committee must be obtained, in accordance with the institutional assurance policies of the U.S. Department of Health and Human Services.

4.3 **Randomization**

This study includes two possible and mutually exclusive randomizations. QARC central review of response is required for EACH of these randomizations. Randomization may occur no sooner than three working days prior to the anticipated start of treatment. Information to document eligibility for randomization will be required at the time of randomization, which will be done through the RDE system.

**Central review of response by QARC is required at two time points: 1) At the end of 2 cycles of ABVE-PC to confirm RER vs. SER status and 2) prior to randomization to ± RT Timely**

**submission of studies to QARC is required to avoid unnecessary delays in therapy. Any therapy delivered that is not consistent with the response categorization as determined at QARC will be considered a major protocol violation. Please contact the study chair if QARC review is delayed >7 days. (See Section 13.5)**

4.31 Eligibility for Randomization to IFRT vs NO IFRT

Patients who are RER after 2 cycles of ABVE-PC, and who are in CR following 2 additional cycles of ABVE-PC (a total of 4 cycles of ABVE-PC), only if confirmed by QARC central review, are randomized to receive consolidative IFRT or not (Standard vs. Reduced therapy). RER patients with less than CR after 4 cycles of ABVE-PC are non-randomly treated with IFRT.

4.32 Eligibility for Randomization to ± DECA x 2

Patients who are SER after 2 cycles of ABVE-PC, as determined by QARC central review, will be randomized between DECAx2 + ABVE-PCx2 + IFRT vs. ABVE-PCx2 + IFRT (Augmented vs. Standard therapy).

## 5.0 TREATMENT PLAN

### 5.1 Initial Treatment

The initial treatment will consist of 2 cycles of ABVE-PC as outlined below. Each cycle is 21 days in duration and commences on Day 1 if the ANC ≥ 750μL (with patients off G-CSF for at least 2 days) and platelets are ≥ 75,000 μL (see Section 6.1). Each cycle of ABVE-PC is as follows:

**ABVE-PC**

Doxorubicin (A)
25 mg/m²/day IV over 10-30 minutes on Day 1 and 2

Bleomycin (B)
5 U/m²/day IV over 10-20 minutes or SQ Day 1
10 U/m²/day IV over 10-20 minutes or SQ Day 8

Vincristine (V)
1.4 mg/m²/day IV push Days 1 and 8 (Maximum dose 2.8 mg)

Etoposide (E)
125 mg/m²/day IV over 1 hour, at a concentration of ≤ 0.4 mg/ml in D5W or NS (utilize standard dilution volumes e.g. 50, 100, 250, 500 ml) Days 1, 2 and 3; avoid use of large volumes of D5W due to potential development of hyponatremia.
*Patients who exhibit a hypersensitivity reaction to Etoposide should be re-challenged with Etoposide phosphate. See Section 6.10 for full details. Study chair and pharmacist must be notified.*

Prednisone (P)
40 mg/m²/day PO divided BID or TID Days 1 - 7 (Round dose to nearest 2.5 mg tablet size)
(IV equivalent may be given if unable to take PO)

**CYCLE 1 only**: Patients who present with need for emergent treatment for respiratory distress or spinal cord compression may receive 4 days of Prednisone prior to completion of diagnostic work-up and before other chemotherapy agents are given. In these cases, a chest X-ray and a CT scan of the neck, chest, abdomen and pelvis must have been performed and if feasible, a biological specimen obtained for definitive diagnosis prior to the administration of Prednisone. The remainder of the diagnostic work-up

should proceed as quickly as tolerated. If oral corticosteroids cannot be tolerated, methylprednisolone may be substituted at equipotent Prednisone doses. The cumulative dose of Prednisone administered for emergent respiratory distress or spinal cord compression should be considered part of the total 280 mg/m² for this cycle. If methylprednisolone was used, the dose should be converted to prednisone-equivalent dose and this should be considered part of the total Prednisone dose noted above.

Cyclophosphamide (C)
800 mg/m² IV over 1 hour in 200ml/m² D5/0.45NS (utilize standard dilution volumes e.g. 50, 100, 250, 500 ml) Day 1. MESNA is not required for this dose of cyclophosphamide, but may be administered at institutional discretion or with hematuria. (See Section 6.3) All patients should receive IV hydration with D51/2NS or NS at 125ml/m²/hour beginning 2 hours prior to cyclophosphamide and continuing for at least 4 hours after cyclophosphamide. Total IV/PO hydration following cyclophosphamide should be 3000 ml/m²/day for at least 8 hours.

GCSF
5 µg/kg/day SQ to start 24 hours after Etoposide and continuing until ANC>1500 $mm^3$ post nadir. **Hold GCSF on Day 8.** Pegylated forms of GCSF such as Neulasta are not permitted.

**Patients must be assessed at this point to evaluate for Slow Early Response, Rapid Early Response or Progressive Disease. (See Section 10.0) THIS REQUIRES CENTRAL REVIEW BY QARC. Timely submission of studies to QARC is required to avoid unnecessary delays in therapy. Any therapy delivered that is not consistent with the response categorization as determined at QARC will be considered a major protocol violation.**

## 5.2 Subsequent Treatment of Rapid Early Responders

### 5.21 Additional Chemotherapy

At the conclusion of 2 cycles of ABVE-PC for patients who have sustained a rapid early response (See response criteria Section 10.1), the subsequent treatment will consist of 2 cycles of ABVE-PC given as outlined in Section 5.1. Each cycle is 21 days in duration and commences on Day 1 if the ANC ≥ 750µL (with patients off G-CSF for at least 2 days) and platelets are ≥ 75,000 µL (see Section 6.1).

### 5.22 Randomization for consolidative radiotherapy

At the conclusion of a total of 4 cycles of ABVE-PC in the rapid early responders, evaluation for complete response is made. (See Section 10.1 for response criteria) Those who have sustained a complete response (CR) will be randomized to receive involved field radiation therapy (IFRT) (Standard therapy) or no further treatment (Reduced therapy). Failure of the investigator to follow through with randomization will be considered a major protocol violation. No randomization to ± RT will be made without QARC review of studies AFTER 2 CYCLES AND AFTER 4 CYCLES OF ABVE-PC. (See Section 13.5 and 13.6) All patients who refuse randomization should be treated with IFRT, as it is considered standard of care. Patients achieving a Very Good Partial Response (VGPR), Partial Response (PR), or Stable Disease (SD) (See Section 10.4) will receive IFRT and patients with progressive disease (PD) (See Section 10.7) will be taken off protocol therapy and treated at their physician's discretion.

5.221
Treatment ends at the completion of 4 cycles of ABVE-PC for those patients who are not randomized to the RT arm.

5.222
For those randomized to receive radiation therapy (Standard arm), radiation therapy should commence approximately 3 weeks after the last day of the 4th cycle of ABVE is completed and when ANC

>1000/mm$^3$ and platelet count >100,000/mm$^3$. If it is delayed more than 1 week, the Study Chair should be informed. (See Section 14.0 for radiation therapy guidelines).

## 5.3 Subsequent Treatment of Slow Early Responders

### 5.31 Additional Chemotherapy

At the conclusion of 2 cycles of ABVE-PC patients who have sustained a slow early response (See response criteria Section 10.0) will be randomized to subsequent treatment with 2 cycles of ABVE-PC given as outlined in Section 5.1 (Standard therapy arm) or 2 cycles of DECA followed by 2 cycles of ABVE-PC (Augmented therapy arm). Each cycle of ABVE-PC and DECA is 21 days in duration and commences on Day 1 if the ANC ≥ 750μL (with patients off G-CSF for at least 2 days) and platelets are ≥ 75,000 μL (see Section 6.1). The cycles of DECA are as follows:

Dexamethasone
10 mg/m² IV over 15 minutes on Day 1 and Day 2, prior to etoposide/cytarabine

Etoposide
100 mg/m² IV over 3 hours on Day 1 and Day 2 as continuous infusion mixed with cytarabine*

Cytarabine
3000 mg/m² IV over 3 hours on Day 1 and Day 2 as continuous infusion mixed with etoposide*

*** Mix together in D5W at an etoposide concentration of ≤ 0.4 mg/ml (or to allow for institutional admixture stability guidelines, may administer as separately as simultaneous infusions)**

Dexamethasone ophthalmic solution
2 drops in each eye q6h on Day 1, Day 2 and Day 3

Cisplatin**
Pre-hydration to achieve Urine SG ≤ 1.010 and Urine Output > 100ml/m²/hour prior to start (Administer oral or IV hydration of 1.5 - 2L/m² over 12 hours or employ similar regimen)
90 mg/m² IV over 6 hours in 1000ml/m² D5W/NS + 10 Gm/m² Mannitol on Day 1 as continuous infusion.

Post-hydration to maintain Urine Output > 65 ml/m²/hour (D5W1/2NS at 125 ml/m²/hr with electrolyte supplementation as required or similar regimen). Wasting of potassium, magnesium, and calcium frequently occur; monitor throughout treatment course and replace as needed.

If decreased Urine Output and no change in weight; consider fluid challenge (10 ml/kg/NS).
If decreased Urine Output and weight gain; consider diuretic therapy.

**Audiometric exam and creatinine clearance at baseline and prior to each course of cisplatin.

GCSF
5 μg/kg/day SQ to start Day 3 and to continue until ANC >1500 mm$^3$ post nadir. Pegylated forms such as Neulasta are not permitted.

### 5.32 Involved field radiation therapy (IFRT) (See Section 14.0 for Radiation Therapy Guidelines)

At the conclusion of all chemotherapy, evaluation for complete response is made (See Section 10.1 for response criteria). Those who have sustained a complete response (CR) or a partial response (PR) will

receive involved field radiotherapy (IFRT). Radiation therapy should commence when ANC >1000/μL and platelet count >100,000/μL approximately 3 weeks after the conclusion of the last cycle of chemotherapy. If it is delayed more than 1 week, the Study Chair should be informed. (See Section 14.0 for radiation therapy guidelines).

Patients with progressive disease (See Section 10.7) will be off protocol therapy and will be treated at their physician's discretion. The Study Chair should be notified.

## 6.0 DRUG DOSE MODIFICATION FOR TOXICITY

### 6.1 Hematologic Toxicity

Full dose chemotherapy should begin on day 21 if the ANC ≥750 μL (with patient off G-CSF for at least 2 days before a cycle of chemotherapy) and platelets are ≥ 75,000 μL. If a patient has not recovered by day 21, check CBC at least twice weekly and begin chemotherapy as soon as hematological recovery is documented. If delay in meeting count criteria is > 1 week, or if a chemotherapy course is delayed > 1 week for reasons other than blood counts criteria.

### 6.2 Hepatic Toxicity

If patient has bilirubin >1.5x upper limit of normal (ULN) when chemotherapy is due to be given, hold chemotherapy and check bilirubin twice weekly until it is < 1.5x ULN.

### 6.3 Hematuria

If gross hematuria occurs with or after cyclophosphamide, subsequent courses should be given with MESNA (400 mg/m² with cytoxan and 400 mg/m² 4 hours after cytoxan) and with hydration at 125ml/m²/hour beginning 2 hours prior to cyclophosphamide and continuing for 4 hours after cyclophosphamide.

### 6.4 Pulmonary

If DLCO in any diffusion capacity test is < 50% of the initial value or predicted value or if both DLCO and FEV/FEV show rapid parallel decrease, obtain blood gases, discontinue further bleomycin.

### 6.5 Cardiac

Patients will get an echocardiogram following 3 cycles of ABVE-PC. If the fractional shortening is < 28%, or the lower limit of institutional normal on 2 successive echocardiograms at least a week apart, the doxorubicin in the 4th cycle of therapy should be held and the Study Chair notified. If at any time the patient develops signs and symptoms of congestive heart failure (i.e. pulmonary or peripheral edema, dyspnea on exertion, poor feeding, increased liver size, deterioration in exercise tolerance or grade IV cardiac toxicity) or prolongation of QTc, which are not attributable to other causes such as sepsis or renal failure, hold doxorubicin and perform repeat ECG and echocardiogram.

### 6.6 Peripheral Neurotoxicity

Vincristine should be held or reduced only for incapacitating peripheral neurotoxicity (e.g. extensive weakness, severe paresthesia, severe ileus). If held, the subsequent dose will be given at a 25% dose reduction.

### 6.7 Grade IV Toxicities

Notify Study Chair immediately for Grade IV toxicity, except hematologic.

### 6.8 Ototoxicity

For Grade II ototoxicity, reduce Cisplatin to 45 mg/m². For Grade III or IV ototoxicity discontinue Cisplatin.

### 6.9 Renal Toxicity

If the calculated creatinine clearance using the Schwartz formula is < 70 mL/min/1.73 $m^2$ hold cisplatin for 1 week. If renal function does not improve, omit cisplatin. If the calculated creatinine clearance using the Schwartz formula is ≥ 70 mL/min/1.73 $m^2$ prior to the next course, cisplatin can be resumed at a 25% dose reduction. If it remains < 70 mL/min/1.73 $m^2$, omit cisplatin.

Schwartz formula:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 $m^2$ or
- A serum creatinine based on age/gender as follows:

| Age | Maximum Serum Creatinine (mg/dL) | |
|---|---|---|
| | **Male** | **Female** |
| 1 month to < 6 months | 0.4 | 0.4 |
| 6 months to < 1 year | 0.5 | 0.5 |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

### 6.10 Hypersensitivity Reaction to Etoposide

If with any dose, patient exhibits signs/symptoms of hypersensitivity reaction (HSR) in relation to administration of etoposide the infusion should be discontinued and appropriate treatment per institutional guidelines initiated. If additional doses of etoposide are scheduled for the patient to complete therapy, Etoposide phosphate (Etopophos) should be substituted at equivalent doses. Pretreatment will consist of patient's first morning scheduled treatment steroid dose (prednisone or dexamethasone according to applicable cycle for patient) and diphenhydramine 1 mg/kg IV or PO. Appropriate monitoring for HSR signs/symptoms should be instituted during the Etoposide phosphate infusion with emergency anaphylactic treatment available. Drug administration should be discontinued and appropriate treatment instituted should a reaction also occur with this product. No further doses of Etoposide or Etoposide phosphate should be attempted.

### 6.11 Dosing for obese patients

It is recommended to adjust dosing of chemotherapy for person≥ 30% above IBW according to the following formula:

(Actual body weight - IBW ) x 40% then add this to IBW and use this as the weight to calculate $M^2$ for dosing chemotherapy agents.

If the patient is not obese, but a large muscular individual, then the actual body weight should be used to calculate doses of chemotherapy agents without a max $M^2$.

# 7.0 REQUIRED OBSERVATIONS

## 7.1 Required Observations

| OBSERVATION | STUDY ENTRY | DURING ABVE-PC | DURING DECA | PRIOR TO RT | AT COMPLETION OF RT | END OF TREATMENT/ FOLLOW-UP |
|---|---|---|---|---|---|---|
| History & Physical | X | X[A] | X[A] | X | | |
| CBC/Differential, ESR, Ferritin, Alkaline phosphatase, Electrolytes, BUN, Creatinine, AST or ALT, Bili | X | X[B] | X[B] | X | | |
| Albumin, LH/FSH, estradiol or testosterone | X | | | | | |
| Creatinine clearance | | | X[B] | | | |
| Free T4, TSH | | | | X | | |
| Biopsy | X | | | | | |
| Bilateral Bone Marrow biopsy | X | X[C] | X[D] | | X[E] | |
| Sperm analysis/banking (recommended) | X | | | | | **See Table 7.4 and Section 16.5** |
| ECG | X | X[F] | | | | |
| ECHO or MUGA | X | X[F] | | | | |
| PFTs, DLCO (not required for children under 7 years old) | X | X[F] | | | | |
| CXR (PA, lateral) | X | X[G] | X[H] | | X[I] | |
| CT chest, neck, abdomen, pelvis | X | X[G] | X[H] | | X[I] | |
| Gallium scintigraphy* | X | X[G1] | X[H] | | X[I] | |
| Bone Scan if IIB and/or bone pain | X | X[G1] | X[H] | | X[I] | |
| Biology Studies and Pathology Review[M] | X | X | X | | X | |
| Audiology Testing | | | X[B] | | | |
| $^{18}$Flurodeoxyglocose (FDG) Imaging* | X | X[J] | X[K] | | X[L] | |

* Either gallium scintigraphy or $^{18}$Flurodeoxyglocose (FDG) Imaging may be used as the nuclear medicine study, but the same modality should be used consistently for any single patient. In institutions that have availability of both modalities, they may both be used at required time points, based upon clinical criteria.

A = Day 1 of each cycle.
B = Prior to each cycle; Alkaline phosphatase and ferritin should only be repeated if abnormal at diagnosis.
C = After 2nd and 4th cycles in Stage IV patients if ⊕ at diagnosis.
D = After 2nd cycle in Stage IV patients if ⊕ at diagnosis.
E = After completion of RT in Stage IV patients if ⊕ at completion of chemotherapy.
F = After 3rd cycle.
G = Between Day 15 and 18 of the 2nd cycle and on approximately Day 21 of the 4th cycle.
G1 = Between Day 15 and 18 of the 2nd cycle if + at diagnosis. For RER or SER not randomized to DECA, repeat after the 4th cycle if not negative between Day 12 and 15 of the 2nd cycle.
H = Prior to 1st cycle and after 2nd cycle; Gallium and bone scans only if ⊕ at diagnosis and prior to 1st cycle.
I = One month after completion of RT if not in CR prior to RT, bone scan only if ⊕ at diagnosis.
J = Between Day 15 and 18 of the 2nd cycle if + at diagnosis. For RER or SER not randomized to DECA, repeat after the 4th cycle if not negative between Day 12 and 15 of the 2nd cycle.
K = Prior to 1st cycle and after 2nd cycle, if positive prior to 1st cycle.
L = One month after completion of RT if not in CR prior to RT.
M = Please see Table below and Section 7.2, 7.3, 7.4, and 16.4 for details of biology studies.

| Specimen Submission for Biology Studies and Pathology Review* | | |
|---|---|---|
| **Time Points** | **Sample Type** | **Amount** |
| Baseline<br>(prior to chemotherapy) | Pathology Materials[1]<br><br>Peripheral blood (SST)<br>Peripheral blood (Heparin) | <br><br>10 mL<br>40 mL (total blood collection of 2 mL/kg with max of 50 mL) |
| Day 8 Cycle 1 ABVE-PC only | Peripheral blood (SST) | 10 mL |
| Day 0 of cycle 3 of ABVE-PC Chemotherapy | Peripheral blood (SST)<br>Peripheral blood (heparin) | 10 mL<br>40 mL (total blood collection of 2 mL/kg with max of 50 mL) |
| Completion of RT | Peripheral blood (SST)<br>Peripheral blood (Heparin) | 10 mL<br>40 mL (total blood collection of 2 mL/kg with max of 50 mL) |
| 1yr. Follow-up | Peripheral blood (SST)<br>Peripheral blood (Heparin) | 10 mL<br>40 mL (total blood collection of 2 mL/kg with max of 50 mL) |
| At relapse (before salvage therapy is started) | Pathology Materials[1]<br><br>Peripheral blood (SST)<br>Peripheral blood (Heparin | 10 mL<br>40 mL (total blood collection of 2 mL/kg with max of 50 mL) |

[1]Pathology specimens should be submitted as per Section 16.0. If consent has been obtained for the Biology studies, the paraffin block will be used for those studies after the diagnosis has been confirmed. If no block is available, 5 additional unstained slides should be obtained for the Biology studies.
*Additional instructions for the collection and shipping of biology specimens are located in section 16.4.

## 7.2 At Study Entry

a. Routine Evaluation

History and physical examination with documentation of sizes and locations of all enlarged lymph nodes.

b. Routine Laboratory Tests

CBC with differential, erythrocyte sedimentation rate, ferritin, electrolytes, BUN, Creatinine, AST or ALT, Bili, albumin, alkaline phosphatase. LH/FSH/estradiol/testosterone should be obtained in Tanner 4 and 5 patients.

c. Bone Marrow

Bilateral bone marrow biopsies are required on all patients at the time of study entry to define the presence or absence of marrow involvement. If bilateral diagnostic marrow biopsies cannot be obtained, Study Chair must be notified.

d. Surgical Biopsy

A biopsy must be performed to confirm the diagnosis and histological subtype of Hodgkin disease. Surgical (laparotomy) staging is discouraged. Patients will be treated by clinical staging. Those with surgical staging only will not be eligible for study.

e. Reproductive Evaluation
Sperm analysis and banking (post pubertal males) is recommended.

f. Cardiac and Pulmonary Evaluation
Cardiac: ECG, echocardiogram or, if not feasible, MUGA scan. PFT's to include Forced Vital Capacity (FVC); Total Lung Capacity (TLC); Functional Residual Capacity (FRC); Carbon Monoxide Diffusing Capacity (DLCO) corrected for anemia, Residual Volume (RV) and Peak Flows (PIF, PEF). (Pulmonary function tests only on patients over 7 years of age).

g. Imaging Studies
Upright chest X-ray PA & lateral, CT scan of the neck, chest, abdomen and pelvis, nuclear medicine imaging (gallium scintigraphy and/or [$^{18}$F]–Fluorodeoxyglucose (FDG) imaging. If both studies are available, both should be done). For patients who complain of bone pain or patients with Stage IIB disease a technetium bone scan should be performed.

h. Biology Studies
Blood and tumor tissue for biology studies should be collected from all who consent to participate in the optional biology portion of this protocol. While biospecimen collection is highly encouraged, patients may refuse collection of specimens and still participate in the therapeutic protocol. The following biospecimens are required from all consenting patients, prior to treatment:

Tumor tissue:
*Snap frozen tissue in OCT*– 0.5 g

*Paraffin embedded material* (representative sample of the block).
If the patient was diagnosed by biopsy before referral to the treating institution, a good faith effort should be made to obtain a representative sample of the tissue block (preferably) or of 5 representative unstained slides. Please see the Pathology Guidelines (Section 15.0) and Specimen Submission (Section 16.0).

Peripheral blood:
A total of 2 mL/kg of blood (max. of 50 mL) should be obtained and placed in the following tubes:
-One 7-10 mL SST (Serum Separator Tube)
-Remainder 10 mL Heparin tubes

*More details about the biology studies may be found in Section 16.4.*

## 7.3 **During Treatment**

### 7.31 ABVE-PC

a. History and Physical Exam Day 1 of each cycle of chemotherapy and as needed

b. Labs: CBC with differential, erythrocyte sedimentation rate, electrolytes, BUN, Creatinine, AST or ALT, Bili, before each chemotherapy cycle. Ferritin and alkaline phosphatase should be repeated only if abnormal at diagnosis.

c. Imaging studies (Upright chest X-ray PA & lateral in patients with large mediastinal masses, CT scan of the neck, chest, abdomen and pelvis, between Day 15 and 18 of the 2$^{nd}$ and at the conclusion of the 4$^{th}$ cycle of of ABVE-PC. Gallium scintigraphy or [$^{18}$F]–Fluorodeoxyglucose (FDG) imaging (whichever nuclear medicine study done at time of study entry) should be done

between Day 15 and 18 of the 2nd cycle of ABVE-PC and if still positive after the 4th cycle of ABVE-PC for RER patients. (For SER patients who receive DECA, all of this imaging should be repeated after the 2nd DECA cycle and then only repeated after the 4th ABVE-PC (cycle 6) if still positive post DECA).

d. Bone marrow biopsies after 2nd and 4th cycles of ABVE-PC in Stage IV patients, if they had bone marrow disease at diagnosis.

e. ECG, echocardiogram or, if not feasible, MUGA scan after the 3rd cycle of ABVE-PC. PFT's after the 3rd cycle of ABVE-PC to include Forced Vital Capacity (FVC); Total Lung Capacity (TLC); Functional Residual Capacity (FRC); Carbon Monoxide Diffusing Capacity (DLCO) corrected for anemia, Residual Volume (RV) and Peak Flows (PIF, PEF). (Pulmonary function tests only on patients over 7 years of age).

f. Biology studies: Peripheral blood will be obtained at the following time points on all patients who have consented to participate in the optional biology studies:

-Peripheral blood 10 mL in a Serum Separator Tube (SST) on Day 8 of the first cycle of ABVE-PC.
-Peripheral blood on Day 0 of the 3rd cycle of ABVE-PC):
-A total of 2 mL/kg of blood (max. of 50 mL) should be obtained and placed in the following tubes: One 7-10 mL SST (Serum Separator Tube)
Remainder 10 mL Heparin tubes

7.32 DECA

a. History and Physical Exam Day 1 of each cycle of chemotherapy and as needed.

b. An audiogram should be performed prior to each cycle.

c. A creatinine clearance should be performed prior to each cycle.

d. Labs: CBC with differential, erythrocyte sedimentation rate, electrolytes, BUN, Creatinine, AST or ALT, Bili, before each chemotherapy cycle. Ferritin and alkaline phosphatase should be repeated if abnormal at diagnosis.

e. Imaging studies (Upright chest X-ray PA & lateral, CT scan of the neck, chest, abdomen and pelvis, Gallium scintigraphy or [$^{18}$F]–Fluorodeoxyglucose (FDG) imaging, bone scan (only if positive at diagnosis) prior to the 1st and after 2nd cycle of DECA. It should be repeated after the 4th cycle of ABVE-PC if it is not normal after the 2nd cycle of DECA.

f. Bone marrow biopsies after 2nd cycle of DECA in Stage IV patients only if they had bone marrow disease at diagnosis.

g. Biology studies: Peripheral blood will be obtained at the following time points on all patients who have consented to participate in the optional biology studies.
-Peripheral blood at the conclusion of 2 cycles of DECA (on Day 0 of the 3rd cycle of ABVE-PC):
-A total of 2 mL/kg of blood (max. of 50 mL) should be obtained and placed in the following tubes: One 7-10 mL SST (Serum Separator Tube)
Remainder 10 mL Heparin tubes

*More details about the biology studies may be found in Section 16.4.*

7.33 Radiation Therapy

a. History and Physical Exam prior to start of radiation therapy and as needed

b. Labs: CBC with differential, erythrocyte sedimentation rate, ferritin prior to start of radiation therapy. T4 (free T4, if possible) and TSH should be done prior to radiation therapy.

c. Imaging studies (Upright chest X-ray PA & lateral, CT scan of the neck, chest, abdomen and pelvis, Gallium scintigraphy and/or [$^{18}$F]–Fluorodeoxyglucose (FDG) imaging, bone scan, (only if positive at diagnosis) one month after completion of radiation therapy if not in complete remission prior to radiation therapy.

d. Bone marrow biopsies after radiation therapy if positive after completion of chemotherapy in Stage IV patients only.

e. Biology studies: Peripheral blood will be obtained at the following time point on all patients who have consented to participate in the optional biology studies:
-Peripheral blood after completion of radiotherapy.
-A total of 2 mL/kg of blood (max. of 50 mL) should be obtained and placed in the following tubes:
One 7-10 mL SST (Serum Separator Tube)
Remainder 10 mL Heparin tubes
*More details about the biology studies may be found in Section 16.4.*

7.4 **At End of Therapy and During Follow-Up**

This therapeutic study is designed to improve both survivorship and long-term outcomes for children and adolescents with Hodgkin disease. Therefore, patients should be followed closely off therapy for both evidence of recurrent disease and for long-term toxicity of therapy. Therefore, to facilitate reporting of late effects, reporting will be required via the COG RDE data system for the most important long-term effects at 0, 1, 3, 5, 7, and 10 years off therapy. As patients may no longer be returning to their treating institution over this period of time, and to obtain important patient self-reported late effects, a patient questionnaire will be completed at the same time. To further facilitate collection of important health outcomes data and decrease lost-to-follow-up rates, we have requested direct contact with patients for late effects follow-up. Patients may indicate on the consent form whether they wish to be contacted directly and participate in the patient questionnaire. The off therapy roadmap below lists the required and recommended off-therapy procedures to monitor both for recurrent disease or late toxicity.

| TIME* | DATE | | GENERAL STATUS | | | TUMOR STATUS | | | TOXICITY EVALUATION | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| In Months | DUE | DONE | PHYSICAL EXAMS | LAB TESTS[2] | LATE EFFECTS REPORTING[3] | CHEST X-RAY | CT[4] | GALLIUM SCAN /FDG | ECHO EKG | PUL FXN | [6]LH, FSH, ESTRADIOL/ TESTOSTERONE /BONE DENSITY | RENAL[7] | T4TSH[8] | BREAST EXAM[9] (females only) |
| 0 | | | X | X | X | | X | X | | | X | X | X | X |
| 3 | | | X | X | | | X | | X | X | | | | |
| 6 | | | X | X | | | X | | | | | | X | |
| 9 | | | X | X | | | X | | | | | | | |
| 12 | | | X | X | X | | X | | X[5] | X | X | X | X | X |
| 15 | | | X | | | | X | | | | | | | |
| 18 | | | X | X | | | X | | | | | | | |
| 21 | | | X | | | X | | | | | | | | |
| 24 | | | X | X | | | X | | | | | X | X | X |
| 30 | | | X | | | X | | | | | | | | |
| 36 | | | X | X | X | | X | | X | X | X | X | X | X |
| 42 | | | X | | | X | | | | | | | | |
| 48 | | | X | X | | | X | | | | | X | X | X |
| 54 | | | X | | | | | | | | | | | |
| 60 | | | X | X | X | X | X | | X | X | | X | X | X |
| 72 | | | X | | | | | | | | X | | X | X |
| 84 | | | X | | X | | | | X | X | | | X | X |
| 96 | | | X | | | | | | | | | | X | X |
| 108 | | | X | | | | | | | | | | X | X |
| 120 | | | X | | X | | | | X | X | X | | X | X |

* Baseline point is the last day of the last chemotherapy course in patients who did not receive radiotherapy OR about six weeks after t the end of radiotherapy for those who receive radiotherapy.

1 - All PE to include BP, plot growth (standing height, sitting height and arm span yearly until growth has ceased), Tanner staging (for all pt. >10 years until stage 5 is achieved), testicular volume, and age-appropriate reproductive/sexual functioning history. Closely examine irradiated areas for signs of skin or other second cancers. (REQUIRED).

2 - CBC and ESR every visit. ALT or AST, BUN, Creatinine, Bilirubin and serum Ferritin at 12 months post chemo (REQUIRED), then annually for 5 years (RECOMMENDED)
At month 12, 2ml/kg (maximum 50 mL) peripheral blood should be drawn. See Section 16.4 for details (REQUIRED IF PATIENTS CONSENT TO BIOLOGY)

3 - Late effects reporting will also require that the treating physician complete the late effects toxicity scale using the Remote Data Entry format at 0, 1, 3, 5, 7 and 10 years off protocol therapy (REQUIRED). Patients will also complete the patient questionnaire (See Separate Data Forms Packet) at the same time points. Discuss potential late effects and preventive measures.

4- Stage I and II disease need CT of the neck and chest, stage III and IV need CT of the neck, chest, abdomen and pelvis. (REQUIRED) at designated times. Once yearly for the first 3 years off therapy, all patients should have CT of the neck, chest, abdomen and pelvis (REQUIRED)

5 - For those who also received thoracic IFRT, 1, 5, 10 and 20 years off therapy, obtain a 24 hour Holter, if available. (RECOMMENDED)

6 - Obtain bone density, if available, at end of therapy and at 5 and 10 years off therapy. (RECOMMENDED) Begin hormonal testing once patient is greater than 12 years/onset of puberty (REQUIRED)

7 - Pts. Receiving Cisplatin or who received abdominopelvic radiation only: If UA ever abnormal, check BUN and Creatinine. If BUN or Creatinine abnormal, obtain Creatinine clearance. If abdomen/pelvis XRT, check BUN, Creatinine and Creatinine clearance at 1 and 5 years.

8 - Serum T4 and TSH levels 0 and 6 months off therapy, then yearly for patients receiving mantle or cervical RT. (REQUIRED)

9 - Begin semiannual breast exam at puberty and instruct in monthly self-exam. (REQUIRED) For patients who received thoracic radiation, begin yearly mammography at age 25 years or 10 years after receiving radiation, whichever occurs first. (RECOMMENDED)

## 8.0 DRUG INFORMATION

### 8.1 **DOXORUBICIN** (Adriamycin®) NSC #123127 (092006)

**Source and Pharmacology**: An anthracycline antibiotic isolated from cultures of Streptomyces peucetius. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH•. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive t½ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal t½ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 ml/min/kg and is predominately by metabolism and biliary excretion. The P450 Cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | nausea, vomiting, pink or red color to urine, sweat, tears and saliva | Hyperuricemia, facial flushing, sclerosis of the vein | Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia | Mucositis (stomatitis and esophagitis), hepatotoxicity | Radiation recall reactions, conjunctivitis and lacrimation |
| **Delayed:**<br>Any time later during therapy | | Cardiomyopathy[1] (CHF occurs in 5-20% @ cumulative doses ≥450mg/m²)(L) | Cardiomyopathy[1] (CHF occurs in <5% @ cumulative doses ≤400mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis |
| **Late:**<br>Any time after completion of treatment | Subclinical cardiac dysfunction | CHF (on long term follow up in pediatric patients) | Secondary malignancy (in combination regimens) |
| **Unknown Frequency and Timing:** Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans. | | | |

[1] ***Risk increases with chest radiation, exposure at a young or advanced age; (L) Toxicity may also occur later.***

**Formulation and Stability:**
Doxorubicin is available as red-orange lyophilized powder for injection in 10mg[1], 20mg[1], 50mg[1], 150mg[2] vials and a preservative free 2mg/ml solution in 10mg[1], 20mg[1], 50mg[1], 75mg[1], 200mg[2] vials.
*[1]: Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben 1 mg per each 10mg of Doxorubicin to enhance dissolution.*
*[2] Multiple dose vial contains lactose, 0.9%NS, HCl to adjust pH to 3.*

Aqueous Solution: Store refrigerated 2° to 8°C, (36° to 46°F). Protect from light. Retain in carton until contents are used.

Powder for injection: Store unreconstituted vial at room temperature 15° to 30°C (59° to 86°F). Retain in carton until contents are used. Reconstitute with preservative-free normal saline to a final concentration of 2mg/ml. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature under normal room light (100 footcandles) and 15 days under refrigeration 2° to 8°C (36° to 46°F). Protect from exposure to sunlight.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

Administer by IV push; by IV side arm into a running infusion; or doxorubicin may be further diluted in saline or dextrose containing solutions and administered by infusion. Protect final preparation from light. Avoid extravasation.

**Supplier:** Commercially available from various manufacturers. See package insert for further information.

8.2 **BLEOMYCIN** (Bleomycin Sulfate, Blenoxane® Bleocin®, Bleocris®, Bleolem®, Bleomicina®, Cytorich®) NSC #125066 (12/20/05)

**Source and Pharmacology**: Bleomycin is a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus.* Of the thirteen identifiable fractions, the main components are Bleomycin A2 and B2. A DNA-binding region and an iron-binding region are present at opposite ends of the molecule. The cytotoxic effects of Bleomycin result from the formation of oxygen free radicals, which then cause single- and double-strand DNA breaks. Bleomycin-mediated DNA damage requires the presence of a redox-active $Fe^{2+}$ metal ion in the presence of oxygen to generate the activated free radical species. Recently it has also become apparent that Bleomycin mediates the oxidative degradation of all major classes of cellular RNAs. The effects of Bleomycin are cell cycle specific, as its major effects are mediated in the $G_2$ and M phases of the cell cycle. In animal studies high concentrations of Bleomycin are found in the skin, lungs, kidneys, peritoneum, and lymphatics. Tumor cells of the skin and lungs have also been found to have high concentrations of Bleomycin in contrast to the low concentrations found in hematopoietic tissue. The low concentrations of Bleomycin found in bone marrow may be related to high levels of Bleomycin degradative enzymes found in that tissue. After IV administration of 15 units/$m^2$ Bleomycin, there is a rapid biphasic disappearance from the circulation. The initial distribution half-life is on the order of 10 to 20 minutes, whereas the terminal half-life is in the range of 2 to 3 hours. Bleomycin is absorbed rapidly after IM injection, and peak blood levels approximately one-third to one-half those achieved after an IV dose are usually reached in 30 to 60 minutes. In patients with normal renal function, 60% to 70% of an administered dose is recovered in the urine as active Bleomycin. In patients with a creatinine clearance of < 35 mL/min, the plasma or serum terminal elimination half-life increases exponentially as the creatinine clearance decreases. It was reported that patients with moderately severe renal failure excreted less than 20% of the dose in the urine.

**Toxicity:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to <5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | High fever (L), chills | Rash (usually in pressure points)(L) | Idiosyncratic reaction similar to anaphylaxis (hypotension, mental confusion, fever, chills, and wheezing), angioedema, nausea, Vomiting, phlebitis, pain at tumor site, malaise |
| **Prompt:** Within 2-3 weeks, prior to the next course | Raynaud's phenomenon, Hyperpigmentation (with pruritis and scratching), Mucositis | Taste impairment, anorexia, Weight loss | Alopecia, onycholysis (dystrophy, shedding, thickening of the nail bed, and darkening of the nail cuticle), thrombocytopenia |
| **Delayed:** Any time later during therapy, excluding the above conditions | | Pneumonitis (dose dependent) (L) | Dyspnea, fine rales, pulmonary fibrosis (dose dependent – increased in combination with XRT and/or $O_2$ resulting rarely in death) (L), scleroderma-like skin changes, in combination with other chemotherapy agents: Coronary artery disease, myocardial infarction, arterial thrombosis, cerebrovascular accidents |
| **Late:** Any time after completion of treatment | | | |
| **Unknown Frequency and Timing** | Fetal toxicities and teratogenic effects of bleomycin have been noted in animals. Administration of intraperitoneal doses of 1.5 mg/kg/day to rats (about 1.6 times the recommended human dose on a unit/m² basis) on days 6-15 of gestation caused skeletal malformations, shortened innominate artery and hydroureter. Bleomycin is abortifacient but not teratogenic in rabbits, at I.V. doses of 1.2 mg/kg/day (about 2.4 times the recommended human dose on a unit/m² basis) given on gestation days 6-18. It is unknown whether the drug is excreted in breast milk. | | |

***(L) Toxicity may also occur later.***

**Formulation and Stability**: Available in 15 and 30 unit vials as Bleomycin sulfate, a white or yellowish lyophilized powder. The sterile powder is stable under refrigeration 2°C (36°F) to8°C (46°F).

**Guidelines for Administration**: (See treatment and dose modification sections of the protocol.)
For IV Administration: Reconstitute to a concentration of 3 or 5 units/ml with normal saline and infuse over a minimum of 10 minutes.
For IM/Sub Q administration: Reconstitute to a concentration of 5 units/ml with normal saline.

*(Bleomycin should not be reconstituted or diluted with D5W or other dextrose containing diluents. When reconstituted in D5W and analyzed by HPLC, Bleomycin demonstrates a loss of A2 and B2 potency that does not occur when reconstituted in 0.9% sodium chloride.*) Bleomycin is stable for 24 hours at room temperature in Sodium Chloride.

**Supplier:** Commercially available from various manufacturers. See package insert for further information.

### 8.3 **VINCRISTINE SULFATE** (Oncovin®**,** VCR, LCR) NSC #67574 (042006)

**Source and Pharmacology**: Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting mircotubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in

humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | | Jaw pain; headache | Extravasation (rare) but if occurs = local ulceration; shortness of breath and bronchospasm |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Alopecia, constipation, | Weakness, abdominal pain; , mild brief myelosupression (leucopenia, thrombocytopenia, anemia) | Paralytic ileus; ptosis, diplopia, night blindness; hoarseness; vocal cord paralysis; SIADH, seizure; defective sweating |
| **Delayed:**<br>Any time later during therapy | Loss of deep tendon reflexes | Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop; abnormal gait | Difficulty walking or inability to walk; veno-occlusive disease (in combination); blindness, optic atrophy; urinary tract disorders including bladder atony, dysuria, polyuria, nocturia, urinary retention; autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss |
| **Unknown Frequency and Timing:** | Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk. | | |

**Formulation and Stability**:
Vincristine is supplied in a vial each mL of which contains vincristine sulfate, 1 mg (1.08 µmol); mannitol, 100 mg; sterile water for injection; Acetic acid and sodium acetate are added for pH control. The pH of Vincristine Sulfate Injection, USP ranges from 3.5 to 5.5. This product is a sterile solution. Store refrigerated at 2-8˚C or 36-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

**Guidelines for Administration:** See the Treatment and Dose Modifications Sections of protocol.

Injection of vincristine sulfate should be accomplished within 1 minute. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

When dispensed the container or syringe containing vincristine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. Fatal if given intrathecally. For Intravenous use only."

**Supplier**: Commercially available from various manufacturers. See package insert for more detailed information.

8.4 **ETOPOSIDE** (VePesid®, Etopophos®,VP-16) NSC #141540 (112005)

**Source and Pharmacology**: A semisynthetic derivative of podophyllotoxin that forms a complex with topoisomerase II and DNA which results in single and double strand DNA breaks. Its main effect appears to be in the S and $G_2$ phase of the cell cycle. The initial t½ is 1.5 hours and the mean terminal half-life is 4 to 11 hours. It is primarily excreted in the urine. In children, approximately 55% of the dose is excreted in the urine as etoposide in 24 hours. The mean renal clearance of etoposide is 7 to 10 mL/min/m² or about 35% of the total body clearance over a dose range of 80 to 600 mg/m². Etoposide, therefore, is cleared by both renal and non renal processes, i.e., metabolism and biliary excretion. The effect of renal disease on plasma etoposide clearance is not known. Biliary excretion appears to be a minor route of etoposide elimination. Only 6% or less of an intravenous dose is recovered in the bile as etoposide. Metabolism accounts for most of the non renal clearance of etoposide.

The maximum plasma concentration and area under the concentration time curve (AUC) exhibit a high degree of patient variability. Etoposide is highly bound to plasma proteins (~94%), primarily serum albumin. Pharmacodynamic studies have shown that etoposide systemic exposure is related to toxicity. Preliminary data suggests that systemic exposure for unbound etoposide correlates better than total (bound and unbound) etoposide. There is poor diffusion into the CSF < 5%.

Cmax and AUC values for orally administered etoposide capsules consistently fall in the same range as the Cmax and AUC values for an intravenous dose of one-half the size of the oral dose. The overall mean value of oral capsule bioavailability is approximately 50% (range 25-75%).

Etoposide phosphate is a water soluble ester of etoposide which is rapidly and completely converted to etoposide in plasma. Pharmacokinetic and pharmacodynamic data indicate that etoposide phosphate is bioequivalent to etoposide when it is administered in molar equivalent doses.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Nausea, vomiting | Anorexia | Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension) |
| **Prompt:**<br>Within 2-3 weeks, prior to next course | Myelosuppression (anemia, leukopenia), alopecia | thrombocytopenia, diarrhea, abdominal pain, asthenia, malaise, rashes and urticaria | Peripheral neuropathy, mucositis, hepatotoxicity, chest pain, thrombophlebitis, congestive heart failure, Stevens-Johnson Syndrome, exfoliative dermatitis |
| **Delayed:**<br>Any time later during therapy | | | Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails |
| **Late:**<br>Any time after completion of treatment | | | Secondary malignancy (preleukemic or leukemic syndromes) |
| **Unknown Frequency and Timing:** Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20$^{th}$ of the human dose. It is unknown whether the drug is excreted in breast milk. | | | |

**Formulation and Stability**:

Etoposide for Injection is available in sterile multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg etoposide, 2 mg citric acid, 30mg benzyl alcohol, 80 mg modified polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen.

Unopened vials of Etoposide are stable until expiration date on package at room temperature (25°C).

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

Etoposide phosphate must be stored under refrigeration 2°-8°C (36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

Etoposide:
Dilute Etoposide to a final concentration ≤0.4 mg/mL in Dextrose or Normal Saline containing IV solutions.
Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2mg/ml; stability is 24 hours at room temperature with concentrations of 0.4mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4mg/mL. Administer over 30 to 60 minutes. **Do not administer etoposide by rapid intravenous injection.**

To avoid leaching of DEHP from PVC bags and tubing, prepare the Etoposide solution as close as possible preferably within 4 hours to the time of administration or alternatively as per institutional policy, non-PVC containers and tubing may be used.

Etoposide Phosphate:
Dilute the 100 mg vial with 5 or l0 mL of Sterile Water for Injection, USP; 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; Bacteriostatic Water for Injection with Benzyl Alcohol; or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate) respectively.

When reconstituted with diluent containing a bacteriostat, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration at 2˚-8˚C (36˚-46˚F) for 7 days or at controlled room temperature 20˚-25˚C (68˚-77˚F) for 48 hours; following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride USP store at controlled room temperature 20˚-25˚C (68˚-77˚F) for 24 hours.
Following reconstitution, etoposide phosphate may be further diluted to concentrations as low as 0.1 mg/mL etoposide with Dextrose or Saline infusion solutions. Etoposide Phosphate may be administered as a bolus or by IV infusion at rates from 5 to 210 minutes.

**Supplier:** Commercially available from various manufacturers. See package insert for further information.

8.5 **PREDNISONE** (Deltasone, Meticorten, Orasone®, Liquid Pred, Pediapred®, Sterapred®,) NSC #010023 (022006)

**Source and Pharmacology**: Prednisone is a synthetic compound closely related to hydrocortisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Peak blood levels occur within 2 hours of oral intake. Prednisone is approximately 75% protein bound with plasma t½ of 3.2 to 4 hours. (Biologic half-life is 12-36 hours.)

**Toxicity:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to <5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Insomnia, Hyperphagia | Gastritis | Hyperuricemia |
| **Prompt:** Within 2-3 weeks, prior to the next course | immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L) | Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema | Pancreatitis (L), electrolyte imbalance (na retention, hypokalemia, hypocalcemia)(L), increased intraocular pressure (L), hypertension, psychosis, vertigo; headache |
| **Delayed:** Any time later during therapy | Cushing's syndrome (moon facies, truncal obesity) | striae and thinning of the skin, easy bruising, muscle weakness, osteopenia | Spontaneous fractures (L), Growth suppression, Peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L) |
| **Late:** Any time after completion of treatment | | Cataracts (which may be reversible on discontinuation of prednisone in children) | |

***(L) Toxicity may also occur later.***

**Unknown Frequency and Timing:** **Fetal and teratogenic toxicities

** Corticosteroids cross the placenta (prednisone has the poorest transport). In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. Prednisone is excreted into breast milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with prednisone doses ⩽ 20 mg/day.

**Formulation and Stability**: Available in 1, 2.5, 5, 10, 20, 25 and 50mg tablets; liquid, 5mg/5ml or 5mg/ml. Inactive ingredients vary depending on manufacturer but tablet formulations may include: calcium or magniesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. Liquid formulations may include: 5%-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol.

**Supplier:** Commercially available form various sources. See package insert for further information

8.6 **CYCLOPHOSPHAMIDE** (Cytoxan) NSC #26271 (032006)

**Source and Pharmacology:** Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P-450 isoenzymes (CYP2B6, CYP2C9 and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. Cyclophosphamide is well absorbed orally with a bioavailability greater than 75%. The plasma half-life ranges from 4.1 to 16 hours after IV administration and 1.3 to 6.8 hours after oral administration.

**Toxicity:**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Anorexia, nausea & vomiting (acute and delayed) | abdominal discomfort, Diarrhea | Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Leukopenia, alopecia, Immune suppression | Thrombocytopenia, Anemia, Hemorrhagic cystitis (L), | Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, Infection secondary to immune suppression |
| **Delayed:**<br>Any time later during therapy, excluding the above conditions | Gonadal dysfunction : azoospermia or oligospermia (prolonged or permanent)[1] (L) | amenorrhea[1] | gonadal dysfunction : ovarian failure[1] (L)<br>Interstitial pneumonitis, pulmonary fibrosis[2](L), |
| **Late:**<br>Any time after completion of treatment | | | Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis |
| **Unknown Frequency and Timing**: Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects. | | | |

[1] *Dependent on dose, age, gender and degree of pubertal development at time of treatment*
[2] *Risk increased with chest radiation and high dose.*
*(L) Toxicity may also occur later.*

**Formulation and Stability:** Cyclophosphamide for Injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 gm and 2 gm vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25ºC (77ºF) is recommended. The product will withstand brief exposures to temperatures up to 30º C (86ºF).

**Guidelines for Administration:** See Treatment and Dose Modifications sections of the protocol.

Cyclophosphamide for Injection: Reconstitute with sterile water or Bacteriostatic water for injection (paraben preserved only) to a concentration of 20 mg/ml. Solutions reconstituted with preservative should be used within 24 hours if stored at room temperature or within 6 days if stored under refrigeration. If administered as undiluted drug at the 20 mg/ml concentration, reconstitute with NS only to avoid a hypotonic solution.

Cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

**Supplier**: Commercially available from various manufacturers. See package insert for further information

8.7 **DEXAMETHASONE** (Decadron®, Hexadrol®, Dexone®, Dexameth®) NSC #34521 (72006).

**Source and Pharmacology**: Dexamethasone is a synthetic fluorinated glucocorticoid devoid of ineralocorticoid effects. Dexamethasone 0.75 mg has potent anti-inflammatory activity equivalent to approximately 5 mg of prednisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Elimination half-lives for the following age groups have been reported to be: infants and children under 2 years of age - 2.3 to 9.5 hours; 8 to 16 years - 2.82 to 7.5 hours; and adults (age not specified) - 3 to 6 hours. (The Biologic half-life is 36- 72 hours.) It is primarily metabolized in the liver and excreted by the kidneys.

**Toxicity:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to < 5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | Insomnia, Hyperphagia | Gastritis | Hyperuricemia |
| **Prompt:** Within 2-3 weeks, prior to the next course | immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L) | Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema | Pancreatitis (L), increased intraocular pressure (L), hypertension, psychosis, vertigo; headache |
| **Delayed:** Any time later during therapy | Cushing's syndrome (moon facies, truncal obesity) | striae and thinning of the skin, easy bruising, muscle weakness, osteopenia | Spontaneous fractures (L), Growth suppression, Peptic ulcer and GI bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L) |
| **Late:** Any time after completion of treatment | | Cataracts (which may be reversible on discontinuation of dexamethasone in children) | |
| **Unknown Frequency and Timing:** | Fetal and teratogenic toxicities: Dexamethasone crosses the placenta with 54% metabolized by enzymes in the placenta. In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. There are no reports of dexamethasone excretion into breast milk in humans; however, it is expected due to its low molecular weight that it would partition into breast milk. | | |

***(L) Toxicity may also occur later.***

**Formulation and Stability**: Dexamethasone sodium phosphate solution for injection is available as 4 mg/ml, 10 mg/ml, 20 mg/ml and 24 mg/ml. 4 mg of dexamethsone sodium phosphate is equivalent to 3.33 mg of dexamethasone. Vial sizes include 1ml, 5 ml, 10 ml, 25 ml, 30 ml and are available in multi-dose vials as well as unit of use vials and syringes. .Inactive ingredients vary depending on manufacturer but include creatinine, sodium citrate, sodium hydroxide to adjust pH, Water for Injection, sodium sulfite, bisulfite and metabisulfite, methyl and propyl paraben, benzyl alcohol, and EDTA

**Guidelines for Administration:** See Treatment and Dose Modifications section of the protocol.

Dexamethasone sodium phosphate for injection may be given IV, or IM undiluted. For IV use it may be further diluted in dextrose or saline containing solutions. Avoid benzyl alcohol containing dexamethasone solutions for use in neonates. Diluted solutions that contain no preservatives should be used within 24 hours, but maintain stability for at least 14 days in PVC bags at room temperature protected from light.

**Supplier:** Commercially available from various manufacturers. See package insert for further information

8.8 **CISPLATIN** (Cis-diamminedichloroplatinum II, CDDP, cis-DDP, Platinol-AQ) NSC #119875 (032006)

**Source and Pharmacology**: Cisplatin is an inorganic, water-soluble complex containing a central platinum atom, 2 chlorine atoms and 2 ammonia molecules. In aqueous solution, the chloride ions are slowly displaced by water generating a positively charged aquated complex. This activated complex is then available to react with nucleophilic sites on DNA, RNA, or protein resulting in the formation of bi-functional covalent links, very similar to alkylating reactions. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Cisplatin has synergistic cytotoxicity with radiation and other chemotherapeutic agents. Cisplatin has a rapid distribution phase of 25-80 minutes with a slower secondary elimination half-life of 60-70 hours. The platinum from cisplatin, but not cisplatin itself, becomes bound to several plasma proteins including albumin, transferrin, and gamma globulin. Three hours after a bolus injection and two hours after the end of a three hour infusion, 90% of the plasma platinum is protein bound. The complexes between albumin and the platinum from cisplatin do not dissociate to a significant extent and are slowly eliminated with a minimum half-life of five days or more. Platinum is present in tissues for as long as 180 days after the last administration. Both cisplatin and platinum are excreted through the kidneys ranging from 10-50%. Fecal elimination is minimal. Cisplatin's penetration into the CNS is poor.

**Toxicities**

| | **Common**<br>Happens to 21-100 children out of every 100 | **Occasional**<br>Happens to 5-20 children out of every 100 | **Rare**<br>Happens to <5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Nausea (L), vomiting (L) | Metallic taste (L) | Anaphylactic reaction ( facial edema, wheezing, tachycardia, and hypotension), phlebitis |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Anorexia (L), myelosuppression, Hypomagnesemia (L), high frequency hearing loss (L), Nephrotoxicity (↑ Cr, BUN, Uric Acid) (L) | Electrolyte disturbances (L) (hypocalcemia, natremia, kalemia, & phosphatemia ) Peripheral neuropathy (paresthesias in a stocking-glove distribution) (L) | Vestibular dysfunction, tinnitus (L), rash, seizure (L), elevated liver function tests(L), |
| **Delayed:**<br>Any time later during therapy | | Hearing loss in the normal hearing range | Areflexia, loss of proprioception and vibratory sensation, (very rarely loss of motor function) (L), Optic neuritis, papilledema, cerebral blindness, blurred vision and altered color perception (improvement or total recovery usually occurs after discontinuing), chronic renal failure, deafness |
| **Late:**<br>Any time after completion of treatment | | | Secondary malignancy |
| **Unknown Frequency and Timing**: **Fetal toxicities and teratogenic effects of cisplatin have been noted in animals and cisplatin can cause fetal harm in humans. Cisplatin is excreted into breast milk. | | | |

***(L) Toxicity may also occur later.***

**Formulation and Stability**: Available as an aqueous solution containing 1mg/ml of cisplatin and 9mg (1.54mEq)/ml of sodium chloride in 50ml, 100ml and 200 ml multi-dose non-preserved vials. Store at 15°C-25°C (68-77ºF). **Do not refrigerate**. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. Cisplatin removed from its amber container should be protected from light if not used within 6 hours.

**Guidelines for Administration:** See the Treatment and Dose Modifications Sections of this protocol.

Cisplatin may be further diluted in dextrose and saline solutions provided the solution contains ≥ 0.2% sodium chloride. Dextrose/saline/mannitol containing solutions, protected from light, are stable refrigerated or at room temperature for 24-72 hours but since such admixtures contain no preservative, use within 24 hours.

Needles or intravenous sets containing aluminum parts that may come in contact with cisplatin should not be used for preparation or administration. Aluminum reacts with cisplatin causing precipitate formation and a loss of potency.

**Supplier**: Commercially available from various manufacturers. See package insert for more detailed information.

8.9 **CYTARABINE** (cytosine arabinoside, Ara-C, Cytosar®) NSC #063878 (092006)

**Source and Pharmacology**:

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase t½ of about 10 minutes, with a secondary elimination phase t ½ of about 1-3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration.

**Toxicity: (Intravenous, SubQ, IM)**

| | Common<br>Happens to 21-100 children out of every 100 | Occasional<br>Happens to 5-20 children out of every 100 | Rare<br>Happens to <5 children out of every 100 |
|---|---|---|---|
| **Immediate:**<br>Within 1-2 days of receiving drug | Nausea, vomiting, anorexia<br>With High dose:<br>Conjunctivitis | Flu-like symptoms with fever, rash | Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis<br>With High Dose:<br>Cardiomyopathies (vasculitis, and pericarditis), cerebral and cerebellar dysfunction including: encephalopathy, aseptic meningitis, ataxia, dysphasia, nystagmus, a decreased level of consciousness, personality changes, somnolence |
| **Prompt:**<br>Within 2-3 weeks, prior to the next course | Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia)., stomatitis, Alopecia | Diarrhea, hypokalemia, Hypocalcemia, Hyperuricemia<br>With High dose: capillary pulmonary leak syndrome (RDS, pulmonary edema) | Hepatotoxicity, veno-occlusive disease, urinary retention, renal dysfunction,<br>Pain and erythema of the palms and soles |
| **Delayed:**<br>Any time later during therapy, excluding the above conditions | | | Asymptomatic nonoliguric rhabdomyolysis |
| **Unknown Frequency and Timing:** | Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk. | | |

**Formulation and Stability**:
Cytarabine for Injection USP is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. When necessary, the pH of Cytarabine for Injection USP was adjusted with hydrochloric acid and/or sodium hydroxide.
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

**Guidelines for Administration**: See Treatment and Dose Modification sections of the protocol.

**IV Infusion**:
Reconstitute with Bacteriostatic Water for Injection, Dextrose 5% or Normal Saline. May be further diluted with Dextrose or Saline containing solutions for IV infusion. May give by IV bolus injection, by IV infusion or by continuous infusion using the following guidelines:
**High Dose (≥1000 mg/m²/dose):** Dilute in D5W or NS to a convenient volume and infuse over 3 hours. Administer steroid eye drops (dexamethasone or prednisolone), 2 drops each eye q6h beginning immediately before the first dose and continuing 24 hours after the last dose. If patient does not tolerate steroid eye drops may administer artificial tears on the same schedule.

When reconstituted with Bacteriostatic Water for Injection, Cytarabine is stable for 48 hours at room temperature. Use preservative-free cytarabine solutions within 24 hr of reconstitution. Discard if solution appears hazy.

**Supplier:** Commercially available from various manufacturers. See package insert for further information.

8.10 **FILGRASTIM,** (Granulocyte Colony-Stimulating Factor, r-metHuG-CSF, G-CSF, Neupogen®)
NSC #614629 (032007)

**Source and Pharmacology:** Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural protein in that the N- amino acid is methionine and the protein is not glycosylated. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens).The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2 to 8 hours

**Toxicity:**

| | **Common** Happens to 21-100 children out of every 100 | **Occasional** Happens to 5-20 children out of every 100 | **Rare** Happens to <5 children out of every 100 |
|---|---|---|---|
| **Immediate:** Within 1-2 days of receiving drug | | Local irritation at the injection site, headache | Allergic reactions (more common with IV administration than subq):skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea) and cardiovascular (hypotension, tachycardia), low grade fever |
| **Prompt:** Within 2-3 weeks, prior to the next course | Mild to moderate medullary bone pain, | Increased: alkaline phosphatase, lactate dehydrogenase and uric acid, thrombocytopenia | Splenomegaly, splenic rupture, exacerbation of pre-existing skin rashes, sickle cell crises in patients with SCD, excessive leukocytosis |
| **Delayed:** Anytime later during therapy | | | Cutaneous vasculitis, ARDS |
| **Late:** Anytime after completion of treatment | | | MDS or AML (confined to patients with severe chronic neutropenia and long term administration) |
| **Unknown Frequency and Timing:** | Fetal toxicities and teratogenic effects of filgrastim in humans are unknown. Conflicting data exist in animal studies and filgrastim is known to pass the placental barrier. It is unknown whether the drug is excreted in breast milk. | | |

**Formulation and Stability:** Supplied as a clear solution in 300 mcg/ml 1 ml or 1.6 ml vials and prefilled syringes containing 300mcg/0.5mL or 480mcg/0.8mL. Vials are preservative free single use vials. Discard unused portions of open vials. Store refrigerated at 2-8º C (36-46ºF). Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Avoid freezing and temperatures > 30ºC.

For IV use, dilute in D5W **only** to concentrations >15 mcg/ml. At concentrations between 5 and 15 mcg/ml, human serum albumin should be added to make a final albumin concentration of 0.2% (2 mg/ml) in order to minimize the adsorption of filgrastim to infusion containers and equipment. Dilutions of 5mcg/ml or less are not recommended. Diluted filgrastim should be stored at 2-8º C (36-46ºF) and used within 24 hours. **Do not shake.**

**Guidelines for Administration:** See Treatment and Dose Modification sections of the protocol. Filgrastim should not be administered within 24 hours of chemotherapy.

**Supplier:** Commercially available from various manufacturers. See package insert for further information

## 9.0 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. The Study Chair may be called with any questions or problems.

### 9.1 Venous Access

Placement of a central venous access device is strongly recommended, but not required. An infusaport (port-a-cath) is the recommended device. This requires a surgical procedure for which separate consent should be obtained.

### 9.2 Prophylactic Antibiotics

All patients on this protocol should receive prophylaxis for *Pneumocystis carinii* pneumonia (PCP). The first choice for PCP prophylaxis is Trimethoprim-sulfamethoxazole (TMP-SMX) 5 mg/kg/day po divided BID (Maximum dose = 320 mg TMP/day) given 2 consecutive days per week. For those allergic or intolerant to TMP-SMX, Dapsone 1 mg/kg/day po (Maximum dose = 100 mg/day) daily.

### 9.3 Fever and Neutropenia

All patients should be evaluated promptly for fever of 38$^{o}$ C (oral or axilla) three times in a 24 hour period or a single temperature of 38.5$^{o}$ C. If ANC < 500/mm$^{3}$, appropriate cultures should be obtained to rule out an occult invasive bacterial or fungal infection and broad spectrum antibiotics should be given.

Identified specific infections should be treated according to institutional guidelines. Even in the absence of identified infection, antibiotics should be continued until the patient is afebrile > 24 hours and has ANC > 200/mm$^{3}$.

If no etiology is found for the fever, but it persists for seven days, or recurs post initial defervescence while on broad-spectrum antibiotics, antifungal therapy should be added presumptively.

### 9.4 Blood Product Support

9.41 Irradiation
Blood products should be irradiated following the current FDA guidelines found at:
http://www.fda.gov/cber/gdlns/gamma.htm

9.42 Platelets
Indicated for persistent bleeding due to thrombocytopenia, or for a platelet count < 5000/mm$^3$. Some recommend prophylactic platelet transfusions in any patient with a platelet count of less than 20,000 /mm$^3$.

9.43 Red Blood Cells
Indicated for acute blood loss, symptomatic anemia, or for a Hgb < 7 or Hct < 20.

9.44 Granulocytes
Routine granulocyte infusions are not recommended.

9.45 Fresh Frozen Plasma
Indicated for correction of coagulopathy or with severe hepatic dysfunction.

### 9.5 Splenectomy/Splenic Irradiation

All patients undergoing splenectomy or splenic irradiation should be immunized with polyvalent pneumococcal, HIB and meningococcal vaccine (unless received previously). Irradiated spleens left in situ may not be fully functional. For patients who are to have splenectomy, give vaccines prior to splenectomy. Ten to fourteen days prior to laparotomy is optimal if time allows. Penicillin prophylaxis is also recommended for splenectomized patients.

### 9.6 HSV Prophylaxis

Herpes prophylaxis (such as acyclovir 10 mg/kg bid days 5-15) should be administered for those with past history of herpetic stomatitis. Patients with mucositis on therapy should have a viral culture performed and treatment started (acyclovir 750 mg/m²/day IV) if herpes is documented.

### 9.7 General Guidelines

The use of antiemetics and/or analgesics are allowable and encouraged as appropriate during therapy. Additional corticosteroids, including dexamethasone should be avoided as an antiemetic or as a pre-medication for hypersensitivity reaction, as it is an active agent against Hodgkin disease. The daily prednisone dose for ABVE-PC or the dexamethasone dose for DECA may be used for such purposes. Patients must receive appropriate general medical supportive care during therapy to avoid and/or treat infection, nausea and emesis, constipation or diarrhea, dehydration and other side effects of myelosuppressive therapy.

## 10.0 RESPONSE CRITERIA

### 10.1 Summary of Response Criteria Determination

10.11
Response criteria were adapted with some modification from the criteria from the Cotswolds Meeting, the International Workshop to Standardize Response Criteria for Non-Hodgkin Lymphomas, and the RECIST criteria and prior newly diagnosed Hodgkin disease protocols, including CCG 5942, CCG 59704, POG 9425, and POG 9426.[74-76]

10.12
Any node with longest transverse diameter >1.5 cm at the time of diagnosis should be considered compatible with lymphomatous involvement in the absence of a compelling alternative etiology such as infection. This includes supraclavicular, infraclavicular, epitrochlear, brachial, preauricular, and popliteal nodes. Cervical, axillary, inguinal and mesenteric lymph nodes may reach a diameter of 2 cm before being considered involved with lymphoma **if** reactive hyperplasia is considered possible. For specific guidelines and additional considerations regarding assessment of nodal size please refer to Section 3.8 and Appendix I.

10.13
Any focal mass lesion of a visceral organ (such as liver, spleen, kidney) is considered lymphomatous involvement in the absence of reasonable alternative explanation (e.g. cyst, hemangioma, abscess.), unless too small to characterize. Lesions too small to characterize are indeterminate unless follow-up studies allow characterization or tissue sampling is performed.

10.14
A measurable lesion by CT is a lesion that can be accurately measured in two orthogonal dimensions. Nonmeasurable assessable lesions include permeative bone lesions, malignant ascites, malignant effusions, lymphangitic spread, and lesions too small to accurately measure in two dimensions by CT.

10.15
Measurable lesions up to a maximum of 6 lesions in total, representative of all involved organs, will be measured as target lesions at baseline and followed for response. Target lesions will be selected on the basis of size (e.g., largest lesions) and suitability for accurate repeated measurements by imaging or clinical exam. Size is to be recorded using metric notation. Lesion size is expressed as the product of the perpendicular diameters (PPD), and serves as a surrogate measurement of area with dimensions of $cm^2$. The PPD is obtained by multiplying the longest diameter of the lesion by the maximal diameter perpendicular to the longest diameter. The SPPD, or sum of the product of the perpendicular diameters, is obtained by adding the products of the perpendicular diameters of all measurable lesions. All measurable target lesions for response should be listed on the AHOD0031 Hodgkin Disease Staging and Response Worksheet and submitted with imaging studies for central review (See Section 13.5 and Appendix I).

10.16
All non-measurable assessable lesions should be recorded and noted at follow-up. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not greater than 3 weeks before the beginning of treatment. All nonmeasurable lesions should be listed on the AHOD0031 Hodgkin Disease Staging and Response Worksheet and submitted with imaging studies for central review. (See Section 13.5 and Appendix I).

## 10.2 Time Points for Assessing Response

Response will be assessed at the following time points:

10.21
In all patients after 2 cycles of ABVE-PC. Once response is known, perform "call-back" for randomized treatment assignment per Appendix III.

10.22
In all patients, after completion of 4 cycles of ABVE-PC. For RER/CR patients, perform "call back" for randomized treatment assignment per Appendix III.

10.23
In SER group, after completion of 2 cycles of DECA and if still not in CR, after all chemotherapy, prior to RT. If the patient is found to be in CR after the 2nd cycle of DECA, those scans must be sent to QARC at the end of all chemotherapy.If the patient is not in CR after the 2nd cycle of DECA, all imaging studies must be repeated at the end of all chemotherapy (post 4th cycle of ABVE-PC) and submitted to QARC.

10.24
In all patients who receive IFRT, 6 weeks after completion of IFRT only if not in CR at start of radiotherapy.

10.25
In ALL patients, 12 weeks after completion of therapy (chemotherapy or radiation therapy whichever ended last).

## 10.3 CR and VGPR Response Definitions

10.31 Complete Response (CR):

- Resolution of pathologic palpable lymphadenopathy. (For specific guidelines and additional considerations regarding assessment of nodal size, please refer to Appendix I and Sections 3.8 and 10.12).
- At least 80% reduction in the PPD of each of the nodal masses including the mediastinum, or return to normal size with no residual nodal mass greater than 2.0 cm in maximal transverse diameter as measured in the axial plane on CT. Within the mediastinum, a > 2.0 cm residual nodal mass is permissible provided, the PPD has decreased by at least 80%. Individual nodes that were previously confluent must have regressed by more than 80% in their SPPD compared with the size of the original mass.
- Nodal masses that have not regressed at least 80% in their PPD or returned to normal size may reflect residual disease or fibrotic changes and biopsy should be considered.
- Any focal lesions of the liver or spleen or other organ considered due to lymphoma have resolved.
- No residual disease in nonmeasurable assessable lesion sites. (Refer to Sections 3.8, 10.14 and Appendix I for definition).
- No new lesion(s).
- Gallium or FDG negative.

10.32 Very Good Partial Response (VGPR)

- At least 60% reduction in the PPD of each of the areas of measurable disease, or return to normal nodal size, but not constituting a CR.
- Individual nodes that were previously confluent must have regressed by more than 60% in their SPPD compared to the size of the original mass.
- Small nodal masses that have not regressed by at least 60% in their PPD or returned to normal size may reflect lack of VGPR or fibrotic changes.
- No progression of nonmeasurable assessable disease sites.
- No new lesion(s).

## 10.4 RER and SER Definitions

10.41 Rapid Early Response (RER):
Complete Response (CR) or very good partial response (VGPR) following 2 cycles of chemotherapy.

10.42 Slow Early Response (SER):
Less than very good partial response (<VGPR) following 2 cycles of chemotherapy.

**PLEASE NOTE: Only CT (or MRI) scan will be used to define VGPR, RER and SER. Gallium or FDG are not required to be negative for this response determination, but should be performed after 2 cycles of chemotherapy and negativity is required for CR determination.**

10.5 **Partial Response (PR)**

- At least 50% reduction in the PPD of each of the areas of measurable disease, or return to normal nodal size, but not constituting a CR.
- Individual nodes that were previously confluent must have regressed by more than 50% in their SPPD compared to the size of the original mass.
- No progression of nonmeasurable assessable disease sites.
- No new lesion(s).

10.6 **Stable Disease (SD)**

- Less than a partial response but not progressive disease.

10.7 **Progressive Disease (PD) (any of the following)**

- At least 50% increase in the PPD of any of the involved nodes or nodal masses.
- At least 50% increase in the in the PPD of any of the focal organ lesions.
- New lesion(s).
- Progression of a nonmeasurable assessable disease site.

10.8 **Treatment Failure**

- Progressive disease anytime during therapy.
- Less than complete response with biopsy confirmed active disease at the end of therapy.
- Relapse that is biopsy confirmed anytime after the completion of therapy.

## 11.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

11.1 **Criteria for Removal from Protocol Therapy**

a) Progressive disease or relapse;
b) Patient/parent refusal;
c) Completion of all courses of therapy; or
d) Physician's choice.

Removal from protocol therapy for any other reason will be considered a protocol violation. Refusal to randomization for additional chemotherapy and/or consolidative radiation therapy will be considered a protocol violation, if it is at investigator request. Any removal from protocol must be discussed with the Study Chair, even if it is at patient or parent request.

Patients who are off protocol therapy are to be followed until they meet the criteria for off study. (See Section 11.2) Follow-up data will be required until that time.

Patients will have follow up every 6 months until the patient is five years off therapy, then yearly until 10 years after the last patient is enrolled.

### 11.2 Off Study

a) Death;
b) Lost to follow-up;
c) Entry onto another COG therapeutic study;
d) Withdrawal of consent for any further data submission;
e) Second malignant neoplasm; or
f) Tenth anniversary of study closure to accrual.

The Study Chair must be informed if a patient meets any of these off study criteria.

## 12.0 SURGICAL GUIDELINES

### 12.1 Surgical Staging

Surgical staging (laparotomy) is not encouraged or recommended, except for biopsy of a lung or bone lesion. This is supported in the literature, particularly where combined modality therapy is used. In these therapy regimens staging laparotomy would only be marginally useful. All staging is based on the clinical criteria as outlined in Appendix I. The Study Chair should be consulted prior to protocol entry if surgical staging is desired or performed by an individual investigator. Patients who have surgical staging only (without concurrent clinical staging) are ineligible for this protocol.

### 12.2 Lymph Node Biopsy

The objective for the surgeon is to obtain adequate tissue to make a diagnosis, not tumor debulking. The principle is to sample the most accessible nodal region. In the neck, supraclavicular nodes have better diagnostic sensitivity and specificity then those high in the cervical chain. It is important to document prior to surgery the extent and location of any mediastinal disease and the relationship of the disease to any vital structure (particularly the trachea). We strongly recommend obtaining a chest x-ray and CAT scan of the chest prior to biopsy. An open procedure provides the best and safest approach to tissue diagnosis. Fine needle aspiration or Tru-Cut needle biopsies are not adequate for diagnosis by themselves. The largest of the affected lymph nodes should be removed. Lymph nodes that can be removed intact should be used for pathological evaluation. Limiting the use of cautery when dissecting the specimen is encouraged as this will limit histopathology distortion and therefore enhance diagnostic accuracy.

### 12.3 Mediastinal and Lung Disease

Isolated mediastinal disease should be thoroughly evaluated radiographically prior to biopsy. A CT scan or MRI of the thorax is the best method to visualize the mediastinum. Other more accessible areas of disease should be chosen for biopsy whenever possible. It is important to be aware that some large mediastinal masses obstruct the trachea with induction of anesthesia. In these rare cases the surgeon and the oncologist should review all options prior to proceeding with mediastinal biopsy.

A videothorascopic approach for the biopsy is strongly suggested. This is associated with minimal morbidity and high diagnostic accuracy. A limited thoracotomy can also be used, where as mediastinoscopy is almost never required. A median sternotomy should not be used as a biopsy technique. Limiting the use of cautery on the biopsy will reduce artifact and augment the diagnosis. Extranodal Hodgkin disease in the lung parenchyma is best removed by a conservative wedge excision with thin margins. Similar to the lymph node biopsy, placing a central venous catheter at the same time is encouraged if a definitive diagnosis can be made. This will avoid a second surgical procedure later.

### 12.4 Oophoropexy

Prior to abdominal radiation, if the ovaries are in the field of radiation, females should have an oophoropexy to move the ovaries to the midline behind the uterus. Prior to pelvic radiation, the ovaries should be moved to the lateral side walls. This may still result in infertility and patients should be so counseled. Laparoscopic technique is strongly suggested.

### 12.5 Transport of specimens

Specimens should be kept moist with saline and transported immediately to pathology (See Section 16.1). The specimen should NOT be fixed in formalin prior to sending for pathological evaluation.

### 12.6 Surgical procedures during therapy

Data will be collected on all surgical procedures that occur during therapy, other than the initial central venous catheter placement. Data to be collected will include:

- Type of procedure
- Indication for procedure and timing (elective versus emergent)
- Surgical procedures required as a result of therapy complication
- Delays in chemotherapy and/or radiation therapy as a result of the surgical procedure

Surgical recovery and correlation to type and time of cancer therapy will be assessed using this data.

### 12.7 Documentation

All surgical procedures performed in the course of the disease should be reported using the Surgery checklist. If patient was initially diagnosed and underwent biopsy at a non-COG institution, that surgical information should also be recorded on the surgical checklist.

In addition, all operative reports and pathology reports, if applicable, should be submitted for any surgical procedure performed. They will be centrally reviewed to provide information on types of biopsy approaches, optimal and smallest usable amount of tissue to be obtained, and for quality assurance.

## 13.0 RADIOLOGY GUIDELINES

(See Appendix II for detailed radiology guidelines concerning all imaging techniques.)

### 13.1 CT Scan

Helical/spiral CT technique is preferable although conventional axial CT is acceptable. Use of oral and intravenous contrast media is recommended for abdomen and pelvis CT and intravenous contrast media for neck and chest CT. For patients with contrast allergies, renal failure, or other contraindications to the use of intravenous CT contrast media, MRI or non-contrast CT may be used as an alternative imaging modality. In this case, follow-up studies may be performed with the same technique, unless the use of intravenous CT contrast media is permitted by a change in the patient's condition.

### 13.2 Nuclear medicine studies

Two nuclear medicine modalities are acceptable for this study. Choice should be based on institutional availability and clinical criteria. These are gallium scintigraphy and [$^{18}$F]–Fluorodeoxyglucose (FDG) Imaging. Whichever study is used at time of diagnosis should be used at all subsequent evaluation points. As clinically indicated, both studies may be performed.

13.21 Gallium Scintigraphy

**GALLIUM SCINTIGRAPHY, WHILE OBTAINED BETWEEN DAY 15 AND 18 OF THE 2$^{ND}$ CYCLE OF ABVE-PC, SHOULD NOT BE USED IN THE DETERMINATION OF RAPID**

**EARLY RESPONSE, BUT MAY BE USED IN PLACE OF, OR IN ADDITION TO FDG IMAGING AT INITIAL DIAGNOSIS AND TO DETERMINE COMPLETE RESPONSE.**
Gallium should be injected prior to initiation of chemotherapy. Exceptional circumstances may require emergent therapy and therapy should not be delayed in these cases. For these cases, injection of gallium may be performed before chemotherapy or during the administration of emergent Prednisone therapy (See Section 5.1), with scanning after a 72-hour interval to establish the gallium avidity of the primary tumor.

Imaging is recommended 72-96 hours after tracer injection, with consideration for further delayed imaging at 120 hours or even later to allow gastrointestinal activity to clear and increase tumor-to-background ratio. Cathartics may be helpful to reduce abdominal activity due to excreted gallium in the gut. If available, SPECT should be performed routinely to supplement the planar images, and should include the chest, abdomen and pelvis, if possible. Gallium uptake in lymphoma is graded subjectively by convention. No method for quantitatively or semi-quantitatively assessing gallium uptake in lymphoma has been widely adopted.

### 13.22 [$^{18}$F]–Fluorodeoxyglucose (FDG) Imaging

**FDG IMAGING, WHILE OBTAINED BETWEEN DAY 15 AND 18 OF THE 2$^{ND}$ CYCLE OF ABVE-PC, SHOULD NOT BE USED IN THE DETERMINATION OF RAPID EARLY RESPONSE BUT MAY BE USED IN PLACE OF, OR IN ADDITION TO GALLIUM SCINTIGRAPHY AT INITIAL DIAGNOSIS AND TO DETERMINE COMPLETE RESPONSE.**

As with gallium, FDG imaging should be performed prior to initiation of chemotherapy.
Exceptional circumstances may require emergent therapy and therapy should not be delayed in these cases. FDG imaging may follow bone or gallium scintigraphy, or a MUGA study on the same day, or FDG imaging may be performed on the day preceding any of these studies.

The patient should be fasted for at least 4 hours prior to injection of FDG. Plasma glucose should be checked as FDG should only be injected into a normoglycemic patient. Insulin may be used if necessary to achieve normoglycemia. The recommended dosage of FDG is 0.140-0.200 mCi/kg, with a minimum dose of 2 mCi. The patient should drink water or receive intravenous fluids to promote excretion of FDG through the urinary tract. After injection, the patient is kept at rest for 45-60 minutes and imaging is then performed. The patient should void the bladder immediately prior to imaging. The body should be imaged from the top of the ears to the proximal thigh, just below the pubis. Scans should proceed upward from the pelvis to diminish the effects of accumulation of activity in the bladder. If there is suspicion of involvement in the lower extremities, skull, or skull contents, the volume that is imaged may be expanded. Imaging with a dedicated PET camera is preferred, but imaging with a gamma camera adapted for co-incidence imaging is acceptable. FDG activity should be corrected for attenuation, scatter, and radioactive decay. Attenuation correction is necessary, as apparent uptake will otherwise vary with depth of the lesion in the body and the nature of surrounding tissues. The procedure used for attenuation correction should be recorded. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of standardized uptake values (SUV). The SUV method is dependent on body weight and correction of SUV by normalizing for body surface area (BSA) reduces this dependency on body weight. SUV's should be obtained for lesions known to be 1.2 cm or larger in diameter. The SUV should be calculated as $SUV_{BSA}$=ROI activity concentration (nCi/cc) X BSA / injected activity (nCi). The region of interest (ROI) should be carefully drawn around the area of elevated FDG uptake in the lesion to minimize partial volume effects. The BSA is calculated from body mass (kg) and height (cm) using an appropriate algorithm. The $SUV_{BSA}$ for each measured lesion should be recorded and the technique for assessing $SUV_{BSA}$ should be consistent on follow-up studies.

### 13.3 Technetium Bone Scan

Technetium bone scan should be performed for patients who complain of bone pain and for patients with IIB disease. Conventional whole body technique should be used. Additional views of questionable areas should be done including SPECT when appropriate, and posterior oblique rib views should be performed if bony structures of the anterior thorax are visible on the posterior view. Correlative radiography should be used in areas of abnormality to improve specificity.

### 13.4 Measurement of lesions

Measurable lesions should be measured in metric notation and recorded with the longest diameter and the maximal diameter perpendicular to the longest diameter, as measured in the axial plane on CT. Lesion size is then expressed as PPD, the product of these perpendicular diameters, which serves as a surrogate measurement of area with dimensions of $cm^2$. The SPPD, or sum of the product of the perpendicular diameters, is obtained by adding the products of the perpendicular diameters for all measurable lesions. All measurable lesions should be recorded on the AHOD0031 Hodgkin Disease Staging and Response Worksheet and submitted with imaging studies for central review. (See Section 13.5 and Appendix I for further details)

### 13.5 Central Review of Imaging Studies

Central review of images will be performed to validate data reporting for quality assurance. Copies of imaging studies (CT, chest radiograph, gallium scintigraphy, FDG imaging, bone scan) at baseline, after 2 cycles of chemotherapy, and at the completion of chemotherapy, should be submitted to QARC at the end of chemotherapy and prior to the start of radiation therapy. The completed AHOD0031 Hodgkin Disease Staging and Response Worksheets should be submitted with these scans. After the first 2 cycles of chemotherapy, assessment of early response will be made by institutions and then reviewed by QARC, to avoid misclassification. At this time, all studies done at diagnosis and at the end of 2 cycles of ABVE-PC must be submitted to QARC. To avoid delays in chemotherapy, all studies should be sent to QARC by Day 18 of Cycle 2. Local radiology reports should be included if available, but scans may be sent without such reports if the final institutional report is not available, so as to avoid therapeutic delays. At the conclusion of chemotherapy, all studies at the end of chemotherapy should be submitted immediately for review by QARC. Central review will be done rapidly to determine response status at the end of therapy. Only those who are determined by QARC to have sustained a rapid early response followed by a complete response will be eligible for randomization to the no radiotherapy arm. For those patients randomly or non-randomly assigned to receive consolidative radiotherapy, all planning studies must also be reviewed by QARC and approved prior to the commencement of the radiotherapy. Any patient who sustains a relapse following enrollment on this study must have their CT and nuclear medicine scans submitted to QARC at the time of relapse. See Section 14.8 for details regarding studies to be submitted for central and radiotherapy review.

### 13.6 Timeline for submission of radiology studies to QARC for central review

- For all patients, In the last week of cycle 2 of ABVE-PC, and no later than Day 18 of this cycle of ABVE-PC, the institution must send all scans and AHOD0031 Hodgkin Disease Staging and Response Worksheets (done to that point) to QARC (See 14.8), and report early response to 2 cycles via Call-back #1 after QARC review. Early response post 2 cycles of ABVE-PC will be reviewed by QARC in real time. **Timely submission of studies to QARC is required to avoid unnecessary delays in therapy. Any therapy delivered that is not consistent with the response categorization as determined at QARC will be considered a major protocol violation.** QARC will review all films and will submit data regarding their assessment of response, using Call-back #1. This will generate an auto-email to the institution. If there is > 1 week delay in the QARC review, the study chair should be contacted.
- For all RER patients, thought by the institution to be a CR at the completion of the $4^{th}$ cycle of ABVE-PC, the institution must send imaging studies (See Section 14.8) together with the

AHOD0031 Request for Diagnostic Review form to QARC and report response to 4 cycles via Call-back #2. QARC will review all studies with real-time post chemotherapy review prior to +/- RT randomization. and will submit data regarding their assessment of response, using Call-back #2. This will generate an auto-email to the institution. The institution returns to RDE screen for treatment assignment based on QARC assessment.

- For RER patients thought by the institution to be <CR at the end of chemotherapy, they are nonrandomly assigned to proceed with radiotherapy. QARC will NOT conduct a real-time review of those cases UNLESS it is specifically requested by the institution. If the institution wishes such a review they should also send imaging studies (See Section 14.8) together with the AHOD0031 Request for Diagnostic Review form to QARC and request an expedited review. In this case, QARC will review and will submit data regarding their assessment of response, using Call-back #2. This will generate an auto-email to the institution. The institution returns to RDE screen for treatment assignment based on QARC assessment.
- For SER patients, the institution should send all scans to QARC prior to start of radiotherapy, but they will not conduct real-time pre-radiotherapy diagnostic reviews for SER patients. For SER patients randomized to DECA, scans performed at the completion of the 2$^{nd}$ cycle of DECA should be sent to QARC if they indicate the patient to be in CR and thus scans at the conclusion of the 4$^{th}$ cycle of ABVE-PC are not required. Otherwise, for SER patients, scans should be completed at the end of all chemotherapy and sent to QARC.
- At time of relapse for any patient enrolled on the study, all imaging studies done at relapse should be sent to QARC.

From the start of Day 1 chemotherapy for cycle 4 ABVE-PC, the following timeline should be followed to facilitate QARC review and randomization for RER patients, and to prevent protocol violation:

| Day | Action |
|---|---|
| 21-28 | Institution must obtain and submit all required scans following cycle 4 of ABVE-PC and send scans to QARC |
| 28 | Deadline for institution to submit scans to QARC |
| 22-29 | QARC receives and reviews all radiology studies and enters results into RDE |
| 28 -36 | Deadline for QARC to enter results into RDE |
| 29-37 | For all patients, randomly or not randomly assigned to IFRT, institution schedules patient for IFRT (See Section 14.8 for pre-IFRT submission requirements for QARC). |
| 29-42 | IFRT begins |

The address for submission is:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Web: http:\\www.qarc.org

Submission of Diagnostic Imaging data in digital format is preferred over hard copies of films. 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. Institutions with PACS systems can contact QARC regarding installation of the COG Dicommunicator software that manages e-mailing studies securely to QARC. Contact Dicommunicator@QARC.org for further information.

## 14.0 RADIATION THERAPY GUIDELINES

**Radiation therapy for patients on COG protocols can only be delivered at an approved COG RT facility (see Administrative Policy 3.9, April 2004)**

### 14.1 General Principles

Involved field radiation therapy will be given to all patients except for those who achieve a rapid early response after 2 cycles of chemotherapy AND a complete response after 4 cycles of chemotherapy, (see Section 10.41) and are randomized to the investigational arm without IFRT. Patients who refuse randomization will be considered off protocol. Such patients should receive radiation therapy as this represents the standard of care and should be followed for outcome analysis.

### 14.2 Radiation Schedule

#### 14.21 Fractionation and start time

Involved field radiotherapy will consist of 21 Gy in 14 fractions of 1.5 Gy per day. The treatment will be given 5 days per week. All fields shall be treated once each day. The total elapsed treatment time will be 2.8 weeks (14 sessions) for each field.

Treatment should begin within no later than 4 weeks after completion of the last cycle of chemotherapy (DAY 21) provided that blood counts have recovered. No radiotherapy should be performed without QARC review. To facilitate this, follow the schedule for QARC central review in Section 13.6. Criteria to start radiotherapy also include an ANC > 1000 $mm^3$ and platelets >100,000 $mm^3$ prior to treatment for each field. If acceptable counts are not present by six weeks post the completion of chemotherapy, or if radiotherapy is delayed beyond Day 49 of the $4^{th}$ cycle of ABVE-PC, contact the Study Chair and Vice Chair.

#### 14.22 Treatment breaks and blood counts

In general, treatment breaks are discouraged. However, radiation should be held if the ANC is < 500 $mm^3$ or platelets are < 25,000 $mm^3$ and resumed when the ANC is >1000 $mm^3$ and platelets are > 75,000/$mm^3$. It is recommended that hemoglobin be kept above 10 gm/dL during treatment. Patients should be transfused if the hemoglobin falls below 7 gm/dL. The need for treatment breaks due to other acute side-effects are expected to be rare and should be discussed with the Radiation Therapy Study Coordinators. No dose modifications will be planned due to breaks in treatment.

#### 14.23 Supra and subdiaphragmatic disease

Patients requiring radiation both above and below the diaphragm should be treated with sequential rather than concurrent fields. The site of bulkiest involvement should be treated first. The second field should be treated when adequate hematologic recovery has occurred following treatment to the first field (see Section 14.21). For patients with extensive infradiaphragmatic disease, a third sequential field may be necessary.

#### 14.24 Emergency Radiation Therapy

In the very rare instance that emergency radiation therapy is required (for example, in order to improve pulmonary or renal function) please notify one of the Radiation Therapy Study Coordinators. Generally, 6 Gy in 3-7 fractions will be administered. This dose will not be considered in the definitive radiation therapy that is subsequently administered.

## 14.3 Equipment

### 14.31 Modality
Photon radiation shall be used. For certain instances (skin lesions and very superficial lymph nodes) where a single, unopposed beam is applicable (as described in these guidelines), an electron beam may be used. Use of IMRT is not allowed on this study.

### 14.32 Energy
Radiation of megavoltage quality shall be used, preferably accelerator beams with a nominal energy of no less than 4 MV.

### 14.33 Geometry
The distance from the radiation source to the prescription point (see below) shall not be less than 80 cm.

### 14.34 Calibration
All therapy units used for this protocol shall have calibrations verified by the Radiological Physics Center.

## 14.4 Treatment Fields and Techniques
Treatment will be limited to areas of disease defined as involved at presentation. The Gross Tumor Volume will include any lymph node measuring > 1.5cm in a single axis as defined on computer tomography. The Clinical Target Volume (CTV) will be the anatomical compartment defined in the following sections of the protocol. The Planning Target Volume will be a 1.0 cm margin around the CTV to account for patient motion and set-up variability. This can be modified at the discretion of the treating radiation oncologist if there are concerns of extended treatment of normal tissue. Anatomical compartments that are contiguous to involved compartments will also need to be treated if they contain lymph nodes > 1.0cm in size as seen on computer tomography. Please note that gallium studies tend to underestimate the volume of disease that needs to be included in the involved field. Treatment fields must be designed to include the original extent of disease. **Radiation therapy fields that are designed to the response of chemotherapy are not permitted on this study.** An exception to this rule is the mediastinum which is described in Section 14.47. The Radiation Therapy Study Coordinators are available to answer questions regarding the design of target volumes.

### 14.41 Beam orientation
Treatment is to be delivered through balanced (equally weighted) AP/PA parallel opposed fields. There are exceptions for certain sites (such as inguinal nodes), as mentioned in the relevant sections below. Divergent and individually cut blocks are recommended. Multileaf collimators are also allowed.

### 14.42 Treatment Position
The patient may be treated entirely in the supine position, or in the supine position for the anterior fields and the prone position for the posterior fields. Other specific positioning recommendations are mentioned in the relevant sections below.

### 14.43 Unilateral neck
If only the involved neck is being considered for treatment on this study, please note that the protocol specified margins must be followed. In the treatment of children the medial field border nearly always must cross the midline and include all of the vertebral body in order to have the appropriate margin for treatment. The superior border should extend from the midpoint of the chin through the mid-tragus. This should provide at a minimum of 2 cm margin at the tip of the mastoid. The inferior border must be

1.5 cm below the clavicle. Small blocks of the oral cavity and spine are not permitted as they often impose on areas of involvement and do not provide for an adequate margin. The lateral field border should be determined by the most lateral extent of disease on the CT study of the neck.

14.44 Bilateral neck

Both sides of the neck shall be treated with the same head position, shielding, and superior and inferior borders as described in Section 14.43.

14.45 Unilateral axilla

Arms should preferably be positioned akimbo (hands on hips) as the arms-up position may place areas of involvement into the parallax of the humeral head. The CT image is crucial to the design of these fields as interpretation of soft -tissue images can vary among institutions. These field borders, accordingly, will vary based on extent of disease at presentation. Please note that disease in the anterior axillary line resides medial to the lateral chest wall, therefore there is often more of the superior aspect of the lung in the axillary treatment field than a traditional mantle field. The humeral head should be shielded if possible.

14.46 Bilateral axillae

This is a rare presentation (without mediastinal involvement) but fields for each side would be designed as in Section 14.45.

14.47 Mediastinum +/- hila

If the mediastinum is the only site of involvement, a traditional mantle field should not be used. Each axilla should be included only when involved. (This spares a great a deal of breast tissue in girls.) The superior field border should encompass the initial superior extent of disease plus a 2cm margin. The lower border should be placed 2 cm or at least one full vertebral body below the lowest initial extent of disease. The inferior border does not need to extend as low as the diaphragm if disease was never present in this region. The lateral field borders will be treated based on the width of the disease and the mediastinum after chemotherapy, not the width of the original mass (unless this width was due to chest wall* or pleural involvement, in which case it should be included). A 1.5 cm margin should be given on any residual mass and the normal mediastinal contour. **If an extensive region of the chest wall requires treatment, electrons may be used to spare underlying lung tissue.*

The lateral margins of the mediastinal portals should cover the bilateral hila. The lungs should be shielded as much as possible without blocking disease. The right hilar border should allow a 1.5 cm margin lateral to the right heart shadow, and at least a 1.0 cm margin lateral to the large, easily visualized right hilar pulmonary vessels. The low inner border of the lung block should be placed to allow at least a 0.5 cm margin lateral to the right heart shadow, and at least a 1.5 cm margin to the vertebral bodies. The left hilar border can be designed in a manner similar to the right hilar border, but the left hilar pulmonary vessels are usually partially obscured by the heart shadow. Information from the chest CT can be used to aid in design of the left hilar block. The heart, especially the left ventricle, should be shielded as much as possible. For those with extranodal lesions invading the pericardium or lungs, the involved tumor volume at diagnosis (prior to chemotherapy) should be included in the field with a 1.5 cm margin (also See Sections 14.496-497 regarding lung and pericardium).

14.48 Multiple supradiaphragmatic sites

Each site of involvement should be treated in one contiguous field as outlined in the previous sections. Any region that was not involved should be omitted. If all sites are involved, treatment will resemble a traditional mantle field.

14.49 Preauricular lymph nodes

The preferred method for treating this region is with an en face, low energy electron beam. This field should be clinically matched to the AP/PA photon neck field when necessary. An alternate method is to extend the AP/PA photon neck field up to the level of the inferior bony orbit (with the head hyperextended), giving enough medial coverage to encompass the preauricular lymph nodes.

14.491 Waldeyer's ring

Frequently when there is CT evidence of upper neck disease, asymmetry is seen in the region of the tonsil and medial lymph node compartments. Ipsilateral tonsil involvement can generally be treated in the AP-PA neck fields with the protocol specified margins. Base of tongue and/or nasopharyngeal involvement will generally require lateral field therapy with opposed photon beams matched to the AP-PA neck fields. Care should be taken to avoid overlap of the spinal cord.

14.492 Spleen only

Patients with spleen involvement should receive a pneumococcal vaccination prior to beginning radiation therapy. If initially involved, the entire spleen should be treated with a 1.5-2 cm margin to account for respiratory movement. The post-chemotherapy spleen volume should be used, as defined by CT scan. If the paraaortic lymph nodes were not involved, then they do not need to be specifically included. However, the splenic field should extend medially to 1.5 cm beyond the contralateral edge of the vertebral bodies to prevent asymmetric radiation of the spine. Only those vertebral bodies adjacent to the spleen should be included. This will result in treatment of the superior paraaortic lymph nodes even when they were not involved.

14.493 Paraaortic lymph nodes only

The superior edge of the field is generally placed at the insertion of the diaphragm with the inferior border at the level of the aortic bifurcation. Laterally, the fields should cover the initial extent of disease with a 1.5 cm margin or should be at least 2 cm lateral to the vertebral bodies on each side. If the patient had massive disease that has responded well to chemotherapy, the post-chemotherapy volume may be used to determine lateral field borders. The spleen or splenic pedicle should be included with this field with borders as described in the preceding section (14.492). Both kidneys should be outlined on the simulation films and should be shielded from the posterior aspect in order to limit the kidney dose to 15 Gy except in areas where this would block the involved spleen or other sites of disease. At a minimum, two-thirds of each kidney should be kept below a dose of 15 Gy.

14.494 Pelvic lymph nodes

All sites of initial disease within the pelvis should be treated with a 1.5 cm margin. Treatment may be unilateral in cases where there was only initial disease involvement on one side of the pelvis. The typical iliac field matches to the paraaortic field superiorly (if the paraaortic region is treated) or just above the aortic bifurcation (approximately the bottom of L4) if the abdomen was not treated. The lower edge of the field should be 3 cm below the ischium. Again, field borders should be individualized for each patient's extent of disease. The fields should encompass the external, internal, and common iliac lymph nodes as well as the inguinal lymph nodes. (A midline shield should be placed with its superior border at the level of the mid-pelvic brim. Its lateral borders will be the medial borders of the obturator canal; its inferior border will extend to the inferior border of the field.) The iliac crests are shielded avoiding shielding the common and external iliac nodes. Females should have an oophoropexy moving the ovaries out of the field of radiation, to the lateral side walls prior to pelvic radiation therapy, especially when treatment will be bilateral. The male gonads should also be shielded completely. Positioning the patient "frog-legged" and using a clam-shell block is appropriate.

14.495 Inguinal/femoral lymph nodes only
If superficial inguinal and/or femoral lymph nodes are involved in the absence of iliac disease, then treatment may be limited to this region. The depth of the lymph nodes should be carefully measured on a CT scan. If adequate superficial and deep coverage of these nodes can be obtained using only an anterior field with photons or an electron beam of appropriate energy, this is encouraged. The upper border is typically 2 to 3 cm above and parallel to the inguinal fold. Inferiorly, the lower border should parallel the upper border. The medial border should be the medial border of the obturator canal; the lateral border should be the lateral border of the acetabulum. Reference to a pre-chemotherapy CT scan is the best way to ensure that all initial disease is covered with a 1.5 cm margin.

14.496 Lung
If pulmonary parenchyma is involved by apparent hematogenous spread, rather than direct extension of mediastinal disease, the involved lung (or lungs) should be treated. Patients presenting with a malignant pleural effusion should also receive treatment to the involved hemithorax. Lung treatment shall be given through individually fabricated transmission blocks to 50% of the daily dose received by involved nodal fields. The total dose to the whole lung should be 10.5 Gy. The inferior border of the lung fields should be designed to encompass the lowest extent of lung tissue as defined by a PA and lateral chest radiograph or CT scan. If disease > 1 cm persists in the pulmonary parenchyma, please call the Radiation Therapy Study Coordinator for possible supplemental radiation.

14.497 Pericardium
If the pericardium was extensively or diffusely involved at diagnosis (including pericardial effusion), the entire heart is to be treated through transmission blocks to 50% of the daily dose received by the unshielded areas. The total dose to the heart should therefore be 10.5 Gy. If areas of pericardium demonstrate gross residual disease after chemotherapy, please call the Radiation Therapy Study Coordinator.

14.498 Liver
In the rare case of liver involvement, the entire liver is to be treated to 15 Gy using partial transmission blocks. The porta-hepatis and paraaortic lymph nodes should receive the full dose of 21Gy if they are involved. The liver should be defined by CT scan and covered with a 1.5 cm margin. The field should cross the vertebral bodies when necessary to prevent asymmetric irradiation of the spine.

14.499 Solitary Bone
If a solitary bone is involved, it should be treated to 21Gy with a 2 cm margin on the initial extent of disease.

14.4991 Bone Marrow or Multiple Bone Involvement
These sites will not be irradiated as part of the treatment for Stage IV disease.

## 14.5 **Dose calculations**

14.51 Dose definition
The total dose to the prescription point will be 21 Gy in 14 fractions of 1.5 Gy (150 cGy). The absorbed dose shall be expressed in centigray (cGy) to muscle.

14.52 Prescription points
For AP/PA parallel opposed portals the prescription point is defined as a point along the central axis of the opposed beams that is midway between the beam entrance and exit points. In a field where the central axis falls beneath a block, an appropriate off-axis point may be used for calculations. The prescription

point for a single unopposed field (e.g. inguinal electron field) is defined as the point along the central axis at the maximum depth of the target volume. The prescription depth will be recorded and included as part of the Quality Assurance documentation.

14.53 Dose Modifications

Radiation therapy should be interrupted if blood counts fall below the criteria listed in section 14.22. There are no dose compensations to be made if there are splits in the treatment secondary to neutropenia, thrombocytopenia, or any other reason. However, if any single field cannot be completed in 7 weeks, the Radiation Therapy Coordinators should be contacted to consider termination of the therapy.

14.54 Dose rate

No dose rate is specified.

## 14.6 Dose Homogeneity and Reference Points

14.61 Heterogeneity Corrections

For the purpose of this study, inhomogeneity corrections for bone or lung attenuation will not be applied to the dose calculations.

14.62 Dose Uniformity

The dose in the midplane throughout the treatment volume should be within the range of –5% to +7%, of the prescribed dose. Reference points will vary depending upon the volume treated. Suggested points include the mid-neck, mediastinum, supraclavicular fossa, and axilla for supradiaphragmatic fields as well as points superior and inferior to the isocenter for subdiaphragmatic fields. The doses to reference points can be calculated at midplane using standard "irregular field" calculation techniques. When necessary, the appropriate compensating filters or boosting/blocking can be performed in order to achieve the suggested dose uniformity.

14.63 Dose to Radiosensitive Organs

Whenever the kidneys, liver, or lungs are included in the radiation field, the resulting dose to these organs will be calculated as reference points. If shadow or transmission blocks are used, calculations will include the contributions from both the blocked and the unblocked treatment fields. The doses to critical structure points can be calculated at midplane using standard "irregular field" calculation techniques. Dose volume histograms (DVH) may serve as an acceptable alternative to calculating critical structure point doses. These calculations will be recorded and submitted as part of the Quality Assurance documentation.

14.64 Matching fields

Although a low dose is being used to each involved field, precautions will be taken to produce a homogenous dosage between adjoining fields. The gap on the skin surface will be calculated by matching the 50% decrement line of the adjacent field at the midplane. (The 50% decrement line is defined as a central line passing through the point at each depth that is 50% of the central axis dose for that depth). Because the total dose to each area is low (21 Gy), there is no need for a spinal block. However, if one is used, (e.g. at the junction of the mantle and para-aortic field) it should be no bigger than 3 cm in length and 1.5 cm in width.

## 14.7 Normal Tissue Sparing

14.71 Lungs

When the whole lungs are to be included in the treatment area, the total dose to the lung will be limited to 50% of the prescribed dose (i.e., 1050 cGy). This will be accomplished by protecting the lungs with AP

and PA transmission blocks so that the daily dose to the lung is 50% of the daily dose to the unshielded prescription point (i.e., 75 cGy per day). The dose to the lungs will be calculated as a reference point and these calculations submitted as part of the Quality Assurance Documentation.

14.72 Kidneys

When more than 1/3 of either kidney is included in the treatment field, it will be shielded posteriorly at the appropriate time in order to limit the dose to the kidney to 1500 cGy. In this case, the dose to the kidneys will be calculated as a reference point and these calculations submitted as part of the Quality Assurance Documentation.

14.73 Liver

When the liver is included in the treatment field, the right lobe of the liver will be shielded with a transmission block, both anteriorly and posteriorly, for the entire treatment. These blocks will be designed so that the liver receives a total of 15 Gy. This dose will be calculated as a reference point and the calculations submitted as part of the Quality Assurance Documentation.

14.74 Gonads

In all male patients, gonadal shielding of 5 HVL minimum will be used as appropriate. In female patients, since an oophoropexy will be performed, blocks of 5 HVL minimum will be used to shield the ovaries if the pelvis is treated.

14.75 Spinal Cord

Whenever the spinal cord is included in adjacent treatment areas, the field borders will be separated by an appropriate gap on the skin. The gap will be calculated as per section 14.64 and these calculations submitted as part of the Quality Assurance Documentation. Superior and inferior margins of the fields which include the spinal cord should be tattooed.

14.8 **Quality Assurance Documentation**

Review by QARC will be performed towards the end of cycle 2 of ABVE-PC to determine RER/CR status and then at the end of cycle 4 prior to randomization for exclusion of radiotherapy for RER/CR patients, and prior to the start of treatment for each radiotherapy area for all patients, randomly or non-randomly assigned to radiotherapy. If more than one area is being treated, the data for all areas may be submitted together if the investigator wishes, or sequentially, but no area may be treated until the adequacy of the treatment volume has been confirmed by QARC. Also See Section 13.6 for submission of radiology studies for central review to QARC.

**The following data are submitted on all patients following by Day 18 or Cycle 2 of ABVE-PC chemotherapy,:**

- Copies of the CT of the neck, chest, abdomen, and pelvis; gallium scans; FDG imaging; bone scan and upright chest x-ray – PA & Lateral from the following time intervals: Pretreatment (baseline) and performed between Days 15 and 18 of cycle 2 of ABVE-PC chemotherapy.
- Completed AHOD0031 Hodgkin Disease Staging and Response Worksheets to be completed for each CT scan.

**The following data are submitted on RER patients thought to be CR by the treating institution following completion of 4 cycles of ABVE-PC chemotherapy, and no later than Day 28 of cycle 4 ABVE-PC. No patient will be randomized without QARC review:**

- Copies of the CT of the neck, chest, abdomen, and pelvis; gallium scans; FDG imaging; bone scan and upright chest x-ray – PA & Lateral at the conclusion of 4 cycles of ABVE-PC chemotherapy.
- Completed AHOD0031 Hodgkin Disease Staging and Response Worksheets to be completed for each CT scan.

**The following additional data are submitted pre-radiotherapy for all patients to receive radiotherapy:**

- Copies of simulator films and /or digitally reconstructed radiographs (DRR's) for each field.
- A Photograph of the patient in the treatment position with the fields marked and visible in the photograph.
- The RT-1 Dosimetry Summary form, one for each target volume, including required reference point and critical organ doses (Sections 14.6 and 14.7).
- Copies of worksheets and/or printouts used for calculations of monitor settings to give the prescribed dose.
- Calculations for required reference points and critical organ doses.
- **Verification (portal) images must be submitted as soon as they become available, whether prior to, or within one week after the start of radiotherapy.**

**Within one week of the completion of radiotherapy, the following data shall be submitted for <u>all</u> patients:**

- Copies of additional simulation and verification (portal) films for any field modifications made subsequent to the initial reporting of data.
- An RT-1 Dosimetry Summary Form if changes have been made subsequent to initial reporting.
- Copies of calculations performed subsequent to the submission of the initial reporting.
- The RT-2 Radiotherapy Total Dose Record form.
- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas, critical organ and reference points.

**The following data are submitted on all patients enrolled in AHOD0031 if they sustain a relapse or a second malignancy:** Copies of the CT scans; gallium scans; FDG imaging; bone scans, chest X Rays should be shipped using the institution's courier account. Institutional imaging reports for these required studies should accompany films. These data should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
Web: http:\\www.qarc.org

Questions regarding the dose calculations or documentation should be directed to:

COG Protocol Dosimetrist
Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601
E-mail: Physics@QARC.org

Submission of Diagnostic Imaging data in digital format is preferred over hard copies of films. 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. Institutions with PACS systems can contact QARC regarding installation of the COG Dicommunicator software that manages e-mailing studies securely to QARC. Contact Dicommunicator@QARC.org for further information.

### 14.9 Radiation Therapy Study Coordinators

Any questions regarding the radiotherapy section of this protocol should be directed to:

Suzanne Wolden, MD
Department of Radiation Oncology
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021
Phone: 212-639-5148
e-mail: woldens@mskcc.org

Louis Constine, MD
University of Rochester Cancer Center,
P.O. Box 647
601 Elmwood Ave
Rochester, N.Y. 14642
Fax: 585-1531
Phone: 585-275-5622
e-mail: Louis_Constine@URMC.Rochester.edu

### 14.10 Definitions of Deviations in Protocol Performance

Prescription Dose:
Minor Deviation: The dose to the prescription point differs from that in the protocol by between 6% and 10%.
Major Deviation: The dose to the prescription point differs from that in the protocol by more than 10%.

Volume:
Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.
Major Deviation: Transection of tumor or potentially tumor bearing area.

## 15.0 PATHOLOGY GUIDELINES

### 15.1 Pathology Goals

1. Provide quality control by central pathologic review with accurate diagnosis and classification of pediatric Hodgkin disease (Hodgkin Lymphoma). This is to be based on both morphologic and immunophenotypic criteria.

2. Employ the Hodgkin disease classification in the World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues, to facilitate concordance in diagnosis.

3. Correlate morphologic and immunophenotypic data for the categories of pediatric Hodgkin disease included in this treatment protocol.

4. Evaluate subtypes of pediatric Hodgkin disease included in this protocol for significant differences in prognosis.

### 15.2 Pathology Central Review

Confirmation of the diagnosis by central pathology review is required for continued inclusion in this study protocol.

#### 15.21 Hodgkin Disease Classification

Morphologic evaluation and classification of the study cases will utilize the criteria described in the WHO Classification.[77] Eligible pediatric Hodgkin disease (lymphoma) cases will be classified into subtypes as:

1. Nodular sclerosis classical
2. Mixed cellularity classical
3. Lymphocyte depleted classical
4. Lymphocyte-rich classical
5. Nodular lymphocyte predominant

#### 15.22 Case Exclusion Criteria

Criteria for case exclusion include:

1. Equivocal immunophenotyping results
2. Morphologically unclassifiable lymphoma
3. Pathology review diagnosis not included in this study

## 16.0 SPECIMEN SUBMISSION

### 16.1 Requirements for Handling Tissue or Cytology Specimens at Primary Institutions

Tissue Specimens

Tissue should preferentially be obtained fresh and delivered immediately to the Pathology Laboratory for optimal handling and distribution.

Submit representative tissue slices for fixation including at least one block with 10% buffered formalin and with the preferred fixative of the institutional pathologist(s). The fixative utilized and length of time in fixative before processing should be indicated for each respective paraffin block. Fixation times should be appropriate for the fixative to allow optimal antigen preservation and immunophenotypic analysis. If sufficient tissue is available, representative fresh tissue should be snap frozen. It is recommended that a minimum of a 5x5x3 mm section of tumor tissue be placed in a plastic cryomold with OCT embedding media covered with corkboard and frozen at -70 degrees Centigrade (utilizing anisopentane bath, liquid nitrogen, or equivalent).

### 16.2 Immunophenotyping Recommendations for Primary Institutions

For eligibility in this protocol, the methodology and criteria for immunophenotypic analysis defined by the submitting institution will be accepted. Recognized methods include: paraffin section, touch imprint or frozen section immunochemistry.

For eligibility in this protocol, a panel of antibodies should be employed for immunophenotypic evaluation. A recommended minimum panel of antibodies should include at least CD45. CD3 (CD45RO),

(UCHL-1), CD20 (L26), CD15 (Leu M1), and CD30 (BerH2, Ki-1), CP79a, CD68, ALK-1, fascin and others also known to be helpful for clarification and differential diagnosis.

If immunophenotyping studies are not available locally, immunophenotyping studies may be performed by the review pathologists on this study.

## 16.3 Specimen Submission for Central Pathology Review

### 16.31 List of Specimen Types

Specimens to be submitted for retrospective pathology review to the COG Biopathology Center include the following:

1. Initial diagnostic material prior to therapy.
2. Bone marrow biopsies with involvement by Hodgkin disease at initial diagnosis.
3. Biopsies at any other time during therapy. These are not required, but should be performed if response status is unclear by physical examination and imaging studies (See Section 10).
4. Specimens demonstrating relapse of Hodgkin disease, or a secondary non-Hodgkin lymphoma at any time.

### 16.32 Materials To Be Submitted

#### 16.321 *Paraffin Blocks*

Submit at least one paraffin block to the COG Biopathology Center. If only one block is available, it is preferable for the block to be prepared in 10% Buffered Formalin. Fixative should be identified for each block. If paraffin blocks cannot be submitted, then submit ten (10) unstained sections (4 microns thick) of unbaked slides air-dried at room temperature for each block. These sections should be place on sialinized slides (i.e. Fisher Superfrost Plus). If the subject has consented to participate in the biology studies, slides not used to confirm the diagnosis will be allocated to those studies.

#### 16.322 *Stained Slides*

Send two H&E stained slides from each diagnostic block.

#### 16.323 Bone Marrow Involved by Hodgkin Disease

If involved, send one representative bone marrow biopsy section (hematoxylin and eosin stain) for review.

#### 16.324 *Pathology Reports*

A copy of all pathology reports on each case should be submitted. This should include:

1. Final reports of diagnostic biopsy and bone marrow specimens;
2. All immunophenotyping reports of diagnostic biopsy and bone marrow specimens (if available);
3. Results of any genotypic studies (i.e. gene rearrangement studies);
4. Results of any cytogenetic (karyotypic) analysis; and
5. Results of any other pertinent studies.

16.325
A Specimen Transmittal form should be completed and submitted along with the above materials. Also, indicate the primary institution pathology diagnosis. The transmittal form can be found in the form packet.

Label all materials with the patient's COG patient identification number and the surgical pathology ID (SPID) number from the corresponding pathology report. Send materials for central pathology review to:

COG Biopathology Center
Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: 614-722-2894
FAX: 614-722-2897

16.33 Paraffin Blocks-Storage/Return
Paraffin blocks will be retained at the COG Biopathology Center unless return is requested by the institution. For cases requiring urgent return of paraffin blocks to the primary institution, the referring institution should contact the COG Biopathology Center to request that initiation of the review process be expedited or blocks be returned immediately after completion of central review. *Please note that for patients who have consented to the Biology studies, representative cores may be obtained for tissue array development from the paraffin blocks prior to return.*

16.4 **Biology Studies and Hodgkin Disease Biospecimen Banking**
With patient consent, peripheral blood and tumor tissue will be collected for use in independently funded approved biology studies that will include analyses of prognostic factors, pathways of molecular pathogenesis, genetic markers of cancer susceptibility and genotoxin exposure. Currently funded and approved studies for specimens collected from patients treated on this protocol include:

- Epstein-Barr Virus (EBV) at diagnosis, during and after therapy in HD;
- Serum cytokine levels including IL10;
- Genetic polymorphisms of drug metabolism enzymes such as glutathione-S-transferases (GSTs) and cytochrome p450;
- Analysis of mutant frequency (Mf) in lymphocytes of HD patients at diagnosis and during therapy using a reporter gene, hypoxanthine phosphoribosyl transferase (*hprt*); and
- Validation of tissue arrays for the histologic analysis of HD.

Additional studies may be proposed by investigators and will be released only after approval by COG HD Committee after review of a formal proposal with appropriate statistical endpoints and documentation of institutional IRB approval or exemption.

**Hodgkin Disease Biospecimen Bank**
The COG provides a major resource for the understanding of HD biology. The Biopathology Center (BPC) will facilitate the distribution of catalogued samples for present and future studies. To eliminate duplication of effort and to optimize utilization of resources, a specific laboratory will perform each assay. The COG HD biology steering committee will review all requests for tumor tissue, and will determine the scientific prioritization for distribution of the laboratory studies. Tissue from this protocol will be available to investigators only after approval according to procedures of the COG HD Committee biology sub-committee. In particular, all studies performed will be directly related to the understanding HD, the etiology of/risk factors for HD, or the effects of HD therapy. Tissues available will include snap frozen tumor, paraffin-embedded tumor, and serum, plasma, and blood cells. The BPC has expertise in

the isolation and preservation of DNA and RNA from tissue samples, and can therefore provide this service efficiently as a central resource for future investigations.

Abstracts and manuscripts detailing results of studies utilizing Tumor Bank material must credit the BPC and the Children's Oncology Group regardless of the affiliation of the principal investigators or authors. Prior to submission of the abstract or manuscript, a copy must be forwarded to the COG Operations Offices and COG HD steering committee for approval and for filing.

COG encourages submission of specimens from all pediatric solid tumor surgeries and of additional biospecimens for use in COG-approved biology research. Such tissue should only be sent in the context of informed consent for tissue banking or for the specific biology studies. The consent form in this protocol has an optional section for consent of biology specimens. For patients who have provided consent for collection, banking or use of biospecimens for research, the following specimens should be sent to the Biopathology Center as follows:

Blood and tumor tissue for biology studies should be collected from all patients who consent to participation in the optional biology studies. While biospecimen collection is highly encouraged, patients may refuse collection of specimens and still participate in the therapeutic protocol. The following biospecimens are required from all patients who consent to the biology study, at the specified time points.

16.41 Materials to be Submitted:

16.411 *Tumor tissue at time of diagnosis*:
Snap Frozen Tissue: At least 0.5 g of tumor tissue should be snap frozen in OCT. Please label the OCT mold with the BPC number prior to freezing.

Paraffin Embedded Material (representative sample of the block).
If the patient was diagnosed by biopsy before referral to the treating institution, a good faith effort should be made to obtain a representative sample of the tissue block (preferably) or of 5 representative unstained slides. Please see the Pathology section 16.12.

16.412 *Peripheral blood:*

***To be drawn at diagnosis, on Day 0 of cycle 3 of ABVE-PC, at the completion of radiotherapy, 1 year off therapy, and at time of relapse prior to salvage regimen.***

Whole blood - A total of 2 mL/kg of blood (max. of 50 mL) should be obtained and placed in the following tubes:

- One 7-10 mL SST (Serum Separator Tube)**
  - This should be spun (for 10 minutes at 2500 rpm at 4°C) prior to shipping to separate serum

  ***If the institution cannot spin the sample in a SST tube prior to shipping, please collect 7-10 ml of blood in a red top tube instead.*
- Place remainder of blood into as many 10 mL green top (Sodium Heparin) tubes as needed.

***To be drawn on Day 8 of cycle 1 of ABVE-PC only.***

- One 7-10 mL SST (Serum Separator Tube)**
  - This should be spun (for 10 minutes at 2500 rpm at 4°C) prior to shipping to separate serum

  ***If the institution cannot spin the sample in a SST tube prior to shipping, please collect 7-10 ml of blood in a red top tube instead.*

***What if a specified time point in missed?***
If biology specimens are not obtained at any requested time point, please send specimens at the next requested time point.

16.42 Specimen labeling
Label all specimens with the BPC Number, collection date and specimen type.

16.43 Specimen Procurement Kits: Specimen Procurement Kits are provided by the Biopathology Center. In order to obtain a Specimen Procurement Kit, call the BPC at 800-347-2486. The kit will contain an OCT mold, foil, slides and the appropriate shipping materials including a Federal Express form pre-billed to the BPC.

16.44 Shipping Information:

16.441 *Transmittal Form*: A Transmittal Form must accompany each shipment of specimens.

16.442 *Packing*: The snap frozen tissue must be sent on dry ice. The Serum Separator Tube (SST) should be wrapped in a cold pack and green top tubes should be sent at room temperature. If a red top is used instead of the SST tube, it should also be wrapped in a cold pack and the package should be marked HANDLE WITH CARE – THIS END UP to prevent hemolysis of the specimen during shipping.

16.443 *Shipping*: Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1-800-238-5355. When requesting pick-up, give the account number on the preprinted air bill, but stress that pick-up is at your institutional address.

The technical staff are available to process specimens Monday – Friday from 8:30 am – 5 pm EST; therefore specimens should only be sent to the BPC Monday through Thursday for Tuesday through Friday delivery. All attempts should be made to obtain and ship the specimen on the same day. If a specimen is obtained and needs to be keep overnight or over a weekend, store the spun SST tube or red top at 4 degrees centigrade ($4^{o}C$) and ship the next possible day, wrapped in an ice pack. The green top tubes may be kept overnight or over a weekend at room temperature and should be shipped at room temperature. Send specimens to:

Biopathology Center
Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2810
Fax: (614) 722-2897

16.45 Summary of Specimen Procurement For Biologic Studies
The BPC will coordinate distribution of tumor and blood samples. This NIH-funded institution has been involved in previous pediatric inter-group biology studies in Wilms' tumor and rhabdomyosarcoma. The BPC will supply kits for the collection of biologic materials upon request.

The kits will include supplies needed for processing the frozen tumor and paraffin embedded material as well as appropriate shipping materials. The BPC will divide the samples and distribute them to the relevant individual laboratories in COG.

### 16.5 Patient Questionnaire

At the conclusion of therapy, and at 1, 3, 5, 7 and 10 years off protocol therapy, in addition to the institution completing the RDE entry for late effects, please have patient complete the questionnaire. The patient should complete the questionnaire at a clinic visit and be given an envelope in which to seal the completed questionnaire. The questionnaire should be completed even if the patient relapses and goes on to additional therapy. Institutional personnel should record their receipt of the questionnaire into the eRDE system and then send the completed questionnaire to the Research Data Center in an outer sealed envelope.

If the patient is not seen at your institution at any of these follow-up dates, contact the Study Chair (dfriedma@fhcrc.org) so that a patient questionnaire may be sent directly to the patient, if they have consented to provide contact information.

## 17.0 STATISTICAL CONSIDERATIONS

### 17.1 Overview

The aim of the statistical design and analysis of this study is to evaluate a response-based approach to therapy of intermediate risk Hodgkin disease. The two primary hypotheses of the study that will be addressed herein are that (1) IFRT can safely be omitted in RER patients who subsequently achieve a CR at the end of chemotherapy; and (2) DECA augmentation of therapy in patients with SER will improve long-term outcome in these patients. Selected secondary hypothesis also will be addressed.

### 17.2 Accrual and study duration

Based on accrual rates from CCG-5942 of 250 Hodgkin Disease (HD) patients per year from former Children's Cancer Group institutions, and the anticipated additional contribution of former Pediatric Oncology Group institutions of at least 60% of this number, the total accrual of HD patients with COG will be at minimum 400 patients per year.

Based on data from CCG-5952, and POG-8625, HD patients will be distributed into three risk categories as show in the table below.

| Risk Group | Percent of Patients | # Patient per year |
|---|---|---|
| Low risk | 33% | 133 |
| Intermediate risk | 54% | 216 |
| High risk | 13% | 51 |
| **Total** | | 400 |

Hence, accrual of intermediate risk Hodgkin disease (IRHD) patients, which are the subject of this study, will be at minimum 210 patients per year. The Dutch Cooperative Group (SKION) joins the study at amendment #2 and expects to enroll 25-30 patients per year. The Israeli group (ISPHO) joins the study at amendment #3 and expects to enroll about 16 patients per year. Prior to amendment #3, the design was to enroll 1150 patients on this study in 5.3 years. Per current amendment #3, the accrual is extended to 1700 eligible patients. To reach the target accrual of 1700, the expected total accrual duration is now about 7.5 years. With amendment #3, the expected accrual for each randomization will be about 320 SER patients randomized to the ±DECAx2, and 640 RER/CR patients that go on study after amendment #1 and are randomized to IFRT/No IFRT.

Because of unavoidable uncertainties in estimates of accrual, RER rates, and CR rates, accrual targets will be reevaluated *without regard to outcome data* at the time of the Data Monitoring Committee meeting closest to the 18th month of the study, after approximately 250 patients have been enrolled. A reevaluation of the feasibility of the study will be performed at that time, with readjustment of accrual and efficacy targets if necessary.

### 17.3 **Study endpoints**

*Efficacy endpoints.* The primary endpoint for efficacy analysis is event-free survival (EFS), which is the minimum time from study entry, time of response assessment, or randomization (as appropriate) until treatment failure (disease progression, disease recurrence, biopsy positive residual after completion of all protocol therapy), occurrence of a second malignant neoplasm, or death from any cause. Secondary efficacy endpoints are overall survival (OS) and disease response.

The patients to be included in the analyses for Aim 1.12 are the cohort of all RER patients who are randomized except those entered the study prior to amendment #1. The patients to be included in the analyses for Aim 1.13 are the cohort of all SER patients who are randomized. These analyses will include randomized patients with protocol violations and randomized patients removed for protocol therapy. However, patients who are determined to be ineligible based on the study eligibility/entry criteria will be excluded.

*Toxicity endpoints.* The primary endpoint for toxicity analysis will be occurrence of any key toxicity, which in this study is the occurrence of any Grade 4 non-hematologic toxicity, or Grade 3 non-hematologic toxicity that doesn't respond to treatment within 7 days despite recommended therapy modification, or toxic death, which is any death primarily attributable to treatment. Exceptions are Grade 3 nausea, vomiting or liver function abnormalities that return to Grade ≤ 2 within 7 days.

All treated patients will be included in the toxicity analyses.

### 17.4 **Strata and Treatment Groups**

Strata
00 = Post-induction response not determined
01 = Rapid Early Responder (RER)
02 = Slow Early Responder (SER)

Treatment Groups
00 = Induction Only
02 = ABVE-PCx2, < CR, IFRT
03 = ABVE-PCx2, CR, IFRT
04 = ABVE-PCx2, CR, No IFRT
05 = ABVE-PCx2 + IFRT + DECAx2
06 = ABVE-PCx2 + IFRT

### 17.5 **Power and precision**

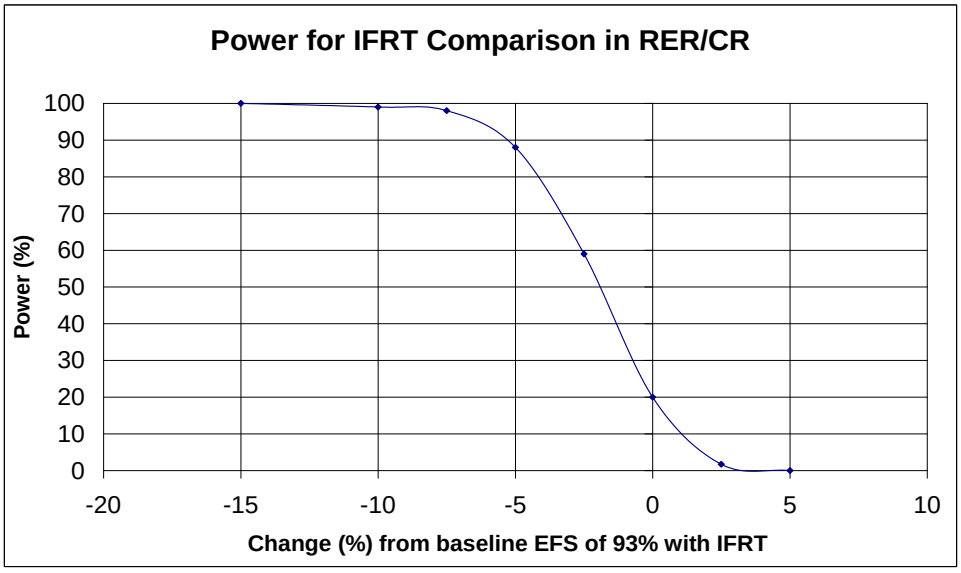
The following assumptions are made in the design of this protocol (followed by necessary changes in amendment #3 if any). The original assumptions in the study design about RER/SER percentages listed below do not agree with the actual percentages observed, amendment (#3) re-estimates the number of patients for each randomized question based on observed numbers.

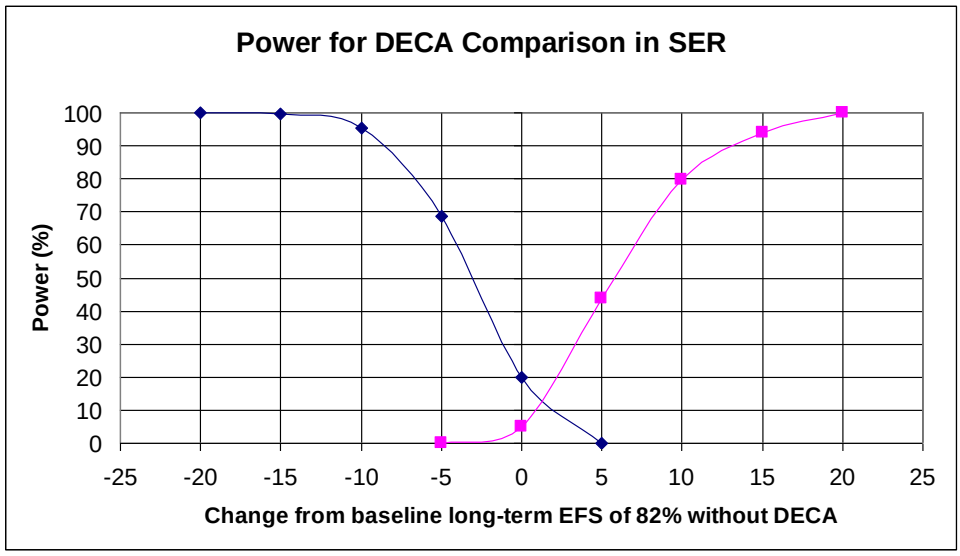
1) 1150 patients will be enrolled on this study in approximately 5.3 years.
   Note: per amendment #3, total target is increased to 1700 with total accrual duration of 7.5 years.
2) Few relapses or other events will occur during the first 3 months of chemotherapy (CRx).

3) The Intermediate risk group will have long-term EFS of 87%, with 7/8 of failures occurring before 3 years.
4) 65% of patients will be rapid early responders (RER) to 2 cycles of ABVE-PCx2. (747 patients)
5) 80% of RER patients will be CR at the end of CRx (598 patients)
   - Long term EFS in this group will be 93% when treated with IFRT.
   - 70% of these patients will be randomized (418 patients).
   - Because of the expected small number of events in this comparison, the IFRT effect, if any, will have a very small influence on the overall outcome of intermediate risk patients.

   Note: per amendment #3, as the total enrollment target is increased to 1700, the total number of patients randomized on IFRT after amendment #1 is expected to be about 640. These patients are included in the analysis of IFRT randomization question.
6) RER patients with less than CR treated with IFRT will have long-term EFS of 90%.
7) 35% of patients will be SER (402 patients) after 2 cycles.
   SER patients will have 82% long-term EFS without augmented therapy.
   85% of these patients will go through with randomization to ±DECAx2. (342 patients)
   Note: per amendment #3, the number of randomized SER patients is estimated to be 320. It is smaller than the original estimate of 342 even though the total accrual target is increased, because the SER percentage on study is about 20% which is much lower than the earlier assumptions.
8) The last patient enrolled will be followed for 1 year.
9) The maximum average loss-to-followup rate will be 2.5%/year.

*Power of the log rank test*. Given the assumptions above, the figures below show the power to detect differences in long-term EFS. The first figure represents the power for a one-sided log rank test to detect a reduction in long-term EFS from the presumed baseline of 93% due to deletion of IFRT in RER/CR patients. Type I error is set at 20%. The second figure represents the power for each of two, one-sided log rank tests for, respectively, a decrease (left curve) and increase (right curve) in long-term EFS from the presumed baseline of 82% due to addition of DECAx2 to standard therapy in SER patients. Type I error is set at 20% for the former comparison and 5% for the latter at the null hypothesis of zero difference. This asymmetrical testing approach is employed because of the expectation that the addition of DECA may result in a non-trivial increase in toxicity, which would only be justified if the addition of DECA actually results in superior long-term EFS. Note that there is a 5% chance of rejecting DECA for lack of efficacy if in fact long-term EFS is improved by 5% with DECA, which for purposes of monitoring is considered the minimum acceptable increase in efficacy to balance the expected increase in toxicity.[78,79]






The cohort of RER/CR patients for IFRT randomization comparison has n=320 for each arm. With total 640 patients, we have about 88% power to detect a 5% decrease from 93% to 88% in a one-sided log rank test with significant level of 0.2. The cohort of SER patients for DECA randomization has n=160 for each arm. With total 320 patients, we have 80% power to detect a 10% increase (82% vs., 92%) in a one-sided log-rank test with a significance level of 0.05.

*Precision of estimates of 4-year EFS.* Since events will be infrequent after 4 years, 4-year EFS is a reasonable surrogate for long-term EFS. Based on 1700 patients entered in total and the assumptions above, the standard error of estimation of 4-year EFS will be approximately as shown in the following table.

| Estimate/Comparison | S.E. for 4-year EFS |
|---|---|
| Overall | ± 1.1% |
| All RER | ± 1.1% |
| RER/CR | ± 1.4% |
| RER/CR – difference± IFRT | ± 2.8%* |
| RER/<CR | ± 1.6% |
| SER | ± 3.0% |
| SER – difference ± DECA x 2 | ± 6.0%* |

**without proportional hazards assumption*

17.6 **Interim Monitoring**

Three separate monitoring rules will be employed, one to look for early compelling evidence that the deletion of IFRT in the RER/CR group is detrimental, and the other two to look for early compelling evidence that the addition of DECA is superior or insufficiently efficacious. Additional monitoring rules for excess toxicity for the DECA-containing arm also will be employed.

*Interim monitoring for IFRT difference in efficacy.* Interim monitoring of the ± IFRT randomization will be based on the one-sided log rank test with 20% type I error described above. Monitoring bounds will be based on the Lan-Demets criterion with $\alpha$-spending function $\alpha t^{2}$.[80] Formal monitoring analyses will be

performed approximately every 12 months. The table below shows the log rank z-values (signed root chi-square statistic) and nominal p-values that will be used.

**Monitoring bounds for IFRT randomization in RER/CR and DECA reduction in efficacy in SER**

| Analysis time | Log rank z-value | Nominal p-value |
|---|---|---|
| Year 1 | -2.76 | 0.003 |
| Year 2 | -2.33 | 0.010 |
| Year 3 | -2.08 | 0.019 |
| Year 4 | -1.83 | 0.034 |
| Year 5 | -1.62 | 0.053 |
| Year 6 | -1.42 | 0.077 |
| Year 7 | -1.26 | 0.104 |
| Year 8.5 | -0.97 | 0.167 |

*Interim monitoring for DECAx2 difference in efficacy*. Interim monitoring of the ± DECAx2 randomization will be based on the two, one-sided log rank tests described above. Monitoring for insufficient efficacy of DECA will utilize the same monitoring bounds presented above. Monitoring for improved efficacy will be based on the Lan-Demets criterion with $\alpha$-spending function $\alpha t^2$ and 5% type I error. Formal monitoring analyses will be performed approximately every 12 months. The table below shows the log rank z-values (signed root chi-square statistic) and nominal p-values that will be used.

**Monitoring bounds for DECA increase in efficacy in SER**

| Analysis time | Log rank z-value | Nominal p-value |
|---|---|---|
| Year 1 | 3.18 | 0.001 |
| Year 2 | 2.82 | 0.002 |
| Year 3 | 2.62 | 0.004 |
| Year 4 | 2.43 | 0.008 |
| Year 5 | 2.27 | 0.012 |
| Year 6 | 2.13 | 0.017 |
| Year 7 | 2.01 | 0.022 |
| Year 8.5 | 1.81 | 0.035 |

*Interim monitoring for DECAx2 difference in key toxicity*.
It is expected that a minority of SER patients who are randomized to standard treatment will experience a key toxicity. A substantial increase in this rate will be considered unacceptable without also compelling evidence of improved efficacy due to the addition of DECA. The test for an increase in key-toxicity rate will be based on a one-sided two-sample test of proportions with 5% type I error, which will provide, for example, approximately 84% power to an increase in key toxicity rate from 15% to 27% when each arm has about 160 patients. Interim monitoring will be performed at the same times as efficacy analyses, using the nominal z-values designated for the improved-efficacy monitoring of the ± DECAx2 comparison. In the event that this interim analysis reveals compelling evidence of increased toxicity due to DECA, then a detailed analysis of the type and severity of the toxicities will be undertaken, with the consideration of treatment modification or study termination.

*Early termination of DECA randomization for lack of efficacy and increased toxicity*
In addition to the three monitoring rules above, conditional power (curtailed testing) calculations will be performed for the test of the hypothesis that the intensification of therapy with DECAx2 is superior within the population of SER patients. This calculation will be performed at the same six-monthly intervals as the other monitoring rules are, but starting only after 20% of the projected number of events have occurred. The method of Cantor[81] will be used to calculate the conditional power based on whatever

data are most currently available. If this analysis, using the protocol-specified failure time model and target difference, demonstrates that the conditional power drops below 10%, then the study will be referred to the DMC for possible closure. A potential drawback to this monitoring rule is the loss of the ability to detect a late treatment difference should the study be closed early.

### 17.7 **Gender and Ethnicity Considerations**

Review of outcome data form previous Hodgkin disease studies indicates that treatment effects are consistent within gender and ethnicity. That is, no one treatment examined has proven superior for one gender or ethnic group. Because of this, the study size will not be adjusted to ensure high power to detect differences in outcome in groups detained by ethnicity or gender.

We will, however, contrast therapeutic outcomes in two situations. First, across subgroups defined by gender, *viz*., males v. females. Second, across subgroups defined by ethnicity, *viz*., white v. black v. hispanic.

Expected Distribution of Patients by Ethnicity/Race and Gender Categories

| | American Indian or Alaskan Native | Asian or Pacific Islander | Black, not of Hispanic Origin | Hispanic | White, Not of Hispanic Origin | Other or Not Reported | Total |
|---|---|---|---|---|---|---|---|
| Female | 4 | 13 | 52 | 73 | 599 | 21 | 762 |
| Male | 4 | 11 | 94 | 112 | 674 | 43 | 938 |
| Total | 8 | 24 | 146 | 185 | 1273 | 64 | 1700 |

### 17.8 **Statistical considerations for biology studies**

This portion of the statistical section addresses the statistical considerations for some of the biology studies currently planned, which will use banked tissue from AHOD0031 patients, who have so consented. Patients on AHOD0031 will be pooled with other Hodgkin disease patients across other therapeutic protocols for some biologic studies, and therefore, this is taken into consideration for statistical power and sample size issues.

#### 17.81 Expected subject accrual

The number of pooled patients expected to be accrued per year and the number with specimens, by patient category, is shown in the Table 17.81A below. These accrual estimates are based on studies CCG-5942, POG-8625, and POG-9426.

Table 17.81A – Annual accrual rates of patients who submit slides or tumor

| Patient Category | Percent of patients | No. of patients per year | No. of pts with slides/blood per yr | No. of pts with blocks per year | No. of pts with tumor per year |
|---|---|---|---|---|---|
| LP | 6% | 24 | 19 | 13 | 10 |
| Low risk | 31% | 133 | 106 | 73 | 53 |
| Intermediate risk | 51% | 216 | 173 | 119 | 87 |
| High risk | 12% | 51 | 41 | 28 | 20 |
| Total | 100% | 424 | 339 | 233 | 170 |
| Total over 5 years | | 2120 | 1695 | 1165 | 850 |

It is estimated that slides will be submitted for 80% of patients, blood will be submitted for 80% of patients, paraffin-embedded blocks of tumor will be submitted for 55% of patients, and tumor will be submitted for 40% of patients. Assuming that if the LP, low, intermediate, and high risk studies are all open at the same time, then an estimated 339 patients per year will have slides, 339 per year will have blood, 233 per year will have blocks, and 170 per year will have tumor. The goal is to have these biologic objectives remain in force for a minimum of five years accrual within each of the patient categories in Table A above. Over 5 years, that would provide 1695 patients to address objectives that need only slides or blood, 1165 patients for objectives that require blocks, and 850 patients for objectives that require tumor.

Due to the lack of a requirement of specimen submission from all patients, there is a potential for collection of specimens from a biased cohort of patients. This will be monitored through a descriptive comparison of the demographic and disease criteria of patients with specimens versus patients without specimens. If there is an apparent bias, modifications to the biology requirements should be considered, including having a separate biology protocol or a means to mandate submission of particular specimens for all patients.

17.82 Biologic studies which currently consider use of specimens from AHOD0031 patients:

- IL-10 serum levels;
- Death Receptor Expression and NF-Kappa B Activity in HD;
- Epstein-Barr Virus (EBV) in HD;
- Genetic polymorphisms in drug metabolism enzymes such as glutathione-S-transferases (GSTs) and cytochrome p450.;
- Analysis of genotoxicity by measurement of mutant frequency (Mf) in lymphocytes using a reporter gene, hypoxanthine phosphoribosyl transferase (*hprt*);
- Validation of tissue arrays for the histologic analysis of HD; and
- Genetic factors associated with development of HD.

17.83 Biologic Endpoints

- Presence or absence of a marker.
- Response to therapy (RER or SER).
- Events: relapse, progression, secondary malignancy, death.

17.84 Power Calculations – justification of number of specimens required

One of the most important and resource-intensive uses for specimens will be in the identification of new marker(s) that are prognostic of outcome. A multivariate Cox Proportional Hazards regression model will be built. The univariate case of this model is the worst-case scenario in terms of the number of specimens required in order to have sufficient power to detect a fixed hazard rate as low as 1.5. Specimens from a total of 1350 patients will be required in order to detect a hazard rate of 1.5 with 80% power in a two-sided test with a 0.05 significance level under the following conditions:

1. The 3-year EFS rate in the inferior group of the new prognostic variable is between 70% and 90%.
2. Patients are allocated between 20% and 80% to each group of the new prognostic variable.

Therefore, with consent, specimens will be requested from each patient participating on this study. More detailed power calculations for particular analyses will be presented in the biology protocol.

17.85 Data Collection and Storage

Specimens will be submitted from the treating institution to the appropriate reference laboratory (usually the BPC) using COG # as the primary identifier. Patient name will not be included unless special consent has been given or if the test results are needed for patient care. Each shipment should include a printed copy of the specimen shipping form after completion of the form on-line via the RDE system. Lab data will be submitted to the RDC via diskette. Only members of the COG statistics department, not reference lab members, will have access to link the lab data to outcomes data. A Virtual Tumor Bank of all specimens will be maintained at the COG RDC, containing data on the type, amount, location, and dates of specimens stored. When specimens are distributed for further research, the virtual bank will record to whom, when, and how much was sent.

The additional clinical data associated with each patient on this study will include treatment protocol, demographics, disease status, response status, and outcome, and will be stored at the COG Research Data Center.

## 18.0 ADVERSE EVENT REPORTING REQUIREMENTS

### 18.1 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.

### 18.2 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 NCI Agent-Specific Adverse Event List (provided in the Drug Information Section of this protocol); or***

- ***the drug package insert (for treatments with commercially available agents).***

18.3 **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 Drug Information Section of this protocol.

- 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.

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning April 1st, 2011 and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

**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 Days[1]

| 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 not due to cancer recurrence must be reported via AdEERS.

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

## 19.0 RECORDS AND REPORTING

### 19.1 Categories of Research Records

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

1. Reference Labs, Biopathology Reviews, and QARC data. These data accompany submissions to these centers, who forward their data electronically to the COG Research Data System.

2. Non-computerized information: Roadmaps, Pathology Narrative Reports, Surgical Reports and Patient Questionnaire. These forms are to be faxed (626-445-4334) or mailed to the Research Data Center. See Section 16.5 for more details about the patient questionnaire.

3. Computerized Information supplied after Registration. All other computerized data will be entered on the COG Remote Data Entry System. This is a secure password controlled system. Upon authentication, you will enter the information, with the aid of schedules and worksheets (essentially paper copies of the RDE screens) as provided in the data form packet. See separate Data Form Packet which includes submission schedule.

### 19.2 **CDUS**

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. 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.

## 20.0 STUDY COMMITTEE

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## APPENDIX I: CLINICAL AND STAGING CRITERIA FOR HODGKIN DISEASE

### A. Stage Grouping

(See the diagram below for definitions of regions.)

Stage I: Involvement of single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

Stage II: Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized contiguous involvement of a single extralymphatic organ or site and its regional lymph node(s) with involvement of one or more lymph node regions on the same side of the diaphragm (IIE).

Stage III: Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized contiguous involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIE+S).

Stage IV: Disseminated (multifocal) involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement.

### B. Symptoms and Presentations

"A" Symptoms: Lack of "B" symptoms.

"B" Symptoms: At least one of the following:

Unexplained weight loss >10%
Unexplained recurrent fever >38°
Drenching night sweats.

### C. Bulk disease

One or both of the following presentations are considered "bulk" disease:

- **Large mediastinal mass:** tumor diameter > 1/3 the thoracic diameter (measured transversely at the level of the dome of the diaphragm on a 6 foot upright PA CXR) In the presence of hilar nodal disease the maximal mediastinal tumor measurement may be taken at the level of the hilus. This should be measured as the maximum mediastinal width (at a level containing tumor and any normal mediastinal structures at the level) over the maximum thoracic ratio.
- **Large extra-mediastinal nodal aggregate:** A continuous aggregate of nodal tissue that measures > 6 cm in the longest transverse diameter in any nodal area

### D. Enumeration of Number of Regions of Nodal Involvement

Each of these twenty regions is counted separately for purposes of determining clinical group.

Peripheral Regions

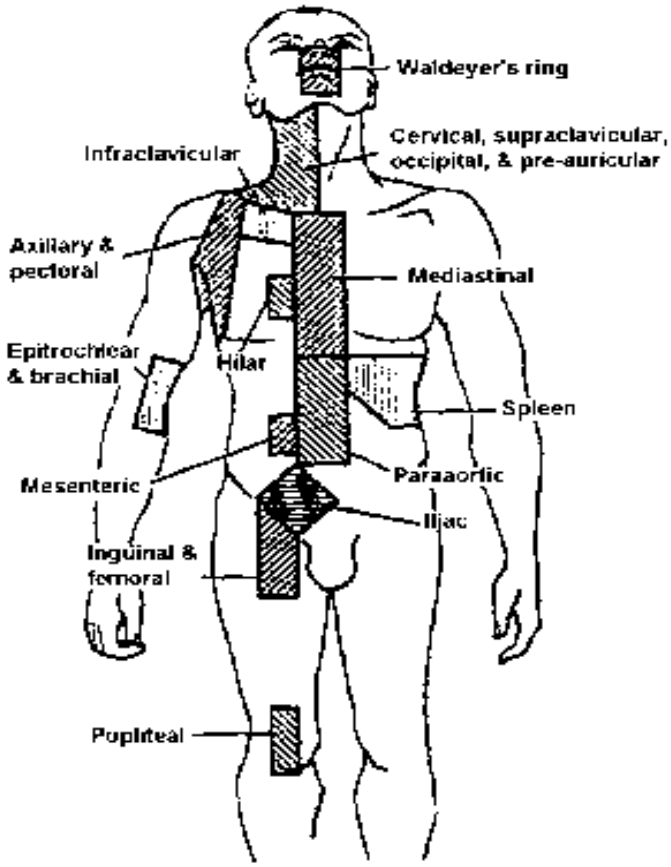
- Right neck; cervical, supraclavicular, occipital, and pre-auricular
- Left neck; cervical, supraclavicular, occipital, and pre-auricular
- Right infraclavicular
- Left infraclavicular
- Right axilla and pectoral
- Left axilla and pectoral
- Right epitrochlear and brachial
- Left epitrochlear and brachial

Central Regions

- Waldeyer's ring (including base of tongue)
- Mediastinum (including paratracheal)
- Hilar
- Mesenteric
- Paraaortic (including retrocrural, portal and celiac)
- Splenic/splenic hilar

Lower Regions

- Right iliac
- Left iliac
- Right inguinal and femoral
- Left inguinal and femoral
- Right popliteal
- Left popliteal




**Anatomical Regions for the Staging of Hodgkin's Disease**

Clinical Criteria for Nodal Involvement – upper torso

The following will be considered Hodgkin disease positive nodes, provided they are not obviously infected.

Any cervical or axillary node > 1.5 cm in longest transverse diameter on physical examination, ultrasound, CT or MRI scan.

- Any cluster of matted or adherent nodes.
- Any enlarged supraclavicular nodes.
- Any mediastinal adenopathy.
- Any Gallium- or FDG-positive nodes.

Clinical Criteria for Nodal Involvement – lower torso

Below the diaphragm the following areas of involvement will be considered positive for Hodgkin disease unless they are pathologically proven to be negative. With the exception of the mesenteric region, nodes > 1.0 cm in the longest transverse diameter should be considered as lymphomatous in the absence of a compelling alternative explanation.

Any Gallium- or FDG-positive nodes, liver or spleen.

- A spleen or liver that has focal defects on CT or ultrasound or MRI. A maximum of 3 target lesions per organ should be measured and will be utilized for response.

**APPENDIX II: RADIOLOGY GUIDELINES**

Imaging Techniques

CT:

Multislice (multidetector) helical (spiral) CT technique is preferred over single slice incremental CT technique. Helical CT technique allows greater anatomic coverage for a given image acquisition time, increasing the volume of tissue imaged during the period of peak contrast enhancement, decreasing the need for sedation, and reducing image degradation from motion artifact. Multislice helical CT scanners permit even more rapid scanning and higher spatial resolution, allowing detection of smaller lesions and the capability for isotropic voxel imaging, facilitating multiplanar image reconstruction for better depiction of the true size dimensions of lesions.

Breath-hold technique should be used in cooperative children to reduce motion artifact and spatial misregistration related to respiration. In children incapable of immobilization, conscious sedation should be considered to minimize image degradation from patient motion. The use of oral and intravenous contrast media is recommended for abdomen and pelvis CT and the use of intravenous contrast material is recommended for neck and chest CT. For patients with iodinated contrast media allergies, renal failure, or other contraindications to the use of contrast media, MRI or non-contrast CT may be used as an alternative imaging modality. For abdomen and pelvic CT scans, oral contrast should be administered at least 45 minutes prior to the exam to allow adequate opacification of the small bowel and prevent misinterpretation of unopacified bowel loops as mass lesions. The dose of oral contrast may vary with the type of contrast available at an institution and the patient age or size. For intravenous contrast, a dose of 1.5-2.0 ml/kg of low osmolar contrast is generally administered in children and adolescents. The rate of contrast injection and the timing of scanning initiation after contrast injection should be selected to maximize the conspicuity of lymph nodes and of lesions involving the solid parenchymal organs, and may vary with the anatomic location of interest and the patient age.

CT image acquisition parameters include beam collimation, detector row configuration, table increment per gantry rotation (pitch), gantry rotation time, image acquisition timing relative to intravenous contrast administration, tube voltage (kVp), and tube current (mA). CT image reconstruction and display parameters include the reconstruction algorithm kernel, reconstructed image slice thickness and spacing, display field-of-view, and window width and level. The available choices for these parameters vary with the CT scanner manufacturer and model, and should be chosen to achieve the best compromise between image quality and patient radiation dose. The use of thinner detector configurations increases spatial resolution for improved detection of smaller lesions, but may incur a greater radiation dose. Reconstructed image slice thickness and spacing should be no greater than 8 mm for evaluation of the chest, abdomen, and pelvis, and no greater than 5 mm for evaluation of the head and neck. Rapid gantry rotation times should be used to reduce scan time and motion artifact. To keep the radiation dose as low as reasonably achievable (ALARA), operator-dependent factors influencing radiation dose, such as the tube current, tube voltage, gantry rotation time, and pitch, should be selected to incur the smallest radiation dose necessary to achieve adequate image quality for diagnostic purposes, and multiphasic studies should be avoided. In general, the smaller and younger the patient, the lower the effective mAs should be. Chest CT exams require lower mAs than abdomen and pelvis CT exams. The peak tube voltage has been traditionally set around 120 kVp, but lower tube voltage may be used to further decrease the radiation dose and increase the contrast to noise ratio for a given radiation dose. Where available, the use of automatic tube current modulation is encouraged to optimize the radiation dose and image quality.

Follow-up studies should be performed with the image acquisition, reconstruction, and display parameters as close as possible to the baseline study. For example, the timing of image acquisition relative to intravenous contrast administration should be consistent across exams, and lesions should be measured at the same window settings and reconstructed image thickness. The minimum measurable lesion size is no

less than double the detector thickness. The size threshold defining a lesion as large enough to characterize or measure is dependent upon multiple factors in addition to actual lesion size, including the attenuation and enhancement pattern of the lesion relative to adjacent tissue, the contrast and spatial resolution of the CT scanning technique, and the diagnostic acumen and confidence of the observer, precluding the use of a single size threshold applicable to all settings. The size dimensions of lesions are traditionally measured in the transverse axial plane, although accurate and precise measurements are feasible in a longitudinal plane if multiplanar coronal or sagittal image reconstructions are generated with helical CT datasets. Measurement of lesions on soft-copy display (e.g., PACS monitor) by electronic caliper is preferred over measurement of lesions on film by hand-held calipers.

Gallium Scintigraphy:
Whenever possible, gallium should be injected prior to initiation of chemotherapy. Exceptional circumstances may require emergent therapy and therapy should not be delayed in these cases. For these cases, injection of gallium may be performed 24 hours before chemotherapy or during the administration of emergent Prednisone therapy, with scanning after a 72-hour interval to establish the gallium avidity of the primary tumor.

Gallium is administered intravenously as Gallium citrate at a dose of 40 -165 uCi/kg, with a minimum total dose of 1.5 mCi and maximum total dose of 10 mCi. Imaging is recommended at 72-96 hours after tracer injection, with consideration for further delayed imaging at 120 hours or even later to allow gastrointestinal activity to clear and increase tumor-to-background ratio. Cathartics may be helpful to reduce abdominal activity due to excreted gallium in the gut.

Image acquisition is performed with medium energy parallel hole collimators with triple pulse height analysis with windows centered on the 93, 184, and 296 keV photopeaks. SPECT acquisition parameters, including counts, time per view, and orbit may vary with equipment features. The image data is processed for display by filtered back projection or an iterative reconstruction algorithm, with a typical image matrix of 64x64 or 128x128.

Planar anterior and posterior whole body images and spot views of the known primary site and suspicious areas on the whole body images should be obtained. SPECT should be performed routinely to supplement the planar images. SPECT imaging provides greater sensitivity than planar imaging, particularly for small or central lesions, and is particularly valuable for separating superimposed normal gallium uptake in the skeleton and soft tissues from uptake in adjacent lesions. SPECT acquisitions should include the chest, abdomen, and pelvis, if possible. Traditionally, gallium uptake in lymphoma is graded subjectively by visual inspection. Semi-quantitative indexes of gallium uptake have been proposed. With these indexes, the degree of uptake is usually judged relative to uptake in the liver, bone marrow, and soft tissue. However, uptake by these normal tissues is variable and sometimes difficult to separate from lesion uptake, limiting accuracy. No method for quantitatively or semi-quantitatively assessing gallium uptake by lymphoma has been widely adopted.

[$^{18}$F]–Fluorodeoxyglucose (FDG) Imaging

As with gallium, FDG imaging should be performed prior to initiation of chemotherapy. Exceptional circumstances may require emergent therapy and therapy should not be delayed in these cases. The patient should be fasted for at least 4 hours prior to injection of FDG. Plasma glucose should be checked and, if the patient is hyperglycemic, appropriate treatment with small doses of insulin should be given to bring the plasma glucose into the normal range.

FDG is administered intravenously at a dose of 0.125-0.200 mCi/kg, with a minimum total dose of 2.0 mCi and maximum total dose of 20.0 mCi. With gamma cameras modified for co-incidence imaging,

there are usually count rate limitations and the maximum total dose may be limited to 5.0-7.5 mCi, depending on the camera. Good hydration is required as the primary route of FDG excretion is renal. The patient should drink water or receive intravenous fluids after injection to promote urinary FDG excretion. After injection, the patient is kept at rest for 45-60 minutes and imaging is then performed. The patient should void the bladder immediately prior to imaging.

The body should be imaged from the top of the ears to the proximal thigh, just below the pubis. Scans should proceed upward from the pelvis to diminish the effects of accumulation of activity in the bladder. If there is suspicion of involvement in the lower extremities, skull or skull contents, the volume that is imaged may be expanded. The 511-annihilation photons, produced by interaction of positrons with electrons, are imaged. Because of the short physical half-life of 1.8 hours and the high photon energy of 511 keV, FDG imaging may follow bone or gallium scintigraphy, or a MUGA study on the same day, or FDG imaging may be performed on the day preceding any of these studies.

Imaging with a dedicated PET camera is preferred, but imaging with a gamma camera adapted for co-incidence imaging is acceptable. If possible, the PET scans should be performed using a 3D acquisition technique. For imaging of the neck, chest, abdomen and pelvis, and areas of known tumor, 360 degree sampling is recommended. Rapid scanning modes that do not involve 360 degree sampling may used to screen other areas of the body that are not known to be involved with tumor. The scan time per table position for the PET emission scan is typically 6-10 minutes. The scan time per table position for the transmission scan is typically 2-4 minutes, with acquisition immediately after the emission scan.

The FDG study is processed for display by filtered back projection or an iterative reconstruction algorithm. FDG activity should be corrected for attenuation, scatter, and radioactive decay. Attenuation correction is necessary, as apparent uptake will otherwise vary with depth of the lesion in the body and the nature of surrounding tissues. The procedure used for attenuation correction should be recorded. The level of tumor uptake is assessed subjectively by visual inspection and semi-quantitatively by determination of standardized uptake values (SUV). Uptake time, glucose levels, and partial volume effects influence both methods. The SUV method is also dependent on body weight and correction of SUV by normalizing for body surface area (BSA) reduces this dependency on body weight. SUV's should be calculated for lesions known to be 1.2 cm or larger in diameter. Smaller lesions may have underestimated SUV's due to partial volume averaging effects at typical scanner resolutions (0.6-1.2 cm). To calculate the SUV, a region of interest (ROI) should be carefully drawn around the area of elevated FDG uptake in the lesion to minimize partial volume effects. The SUV should be calculated as $SUV_{BSA}$=ROI activity concentration (nCi/cc) X BSA / injected activity (nCi). The BSA is calculated from body mass (kg) and height (cm) using an appropriate algorithm. The $SUV_{BSA}$ for each measured lesion should be recorded and the technique for assessing $SUV_{BSA}$ should be consistent on follow-up studies.

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## APPENDIX III: INSTRUCTIONS FOR "CALL-BACKS" FOR RANDOMIZED TREATMENT ASSIGNMENT

Section 4.3 of the protocol details the two, mutually exclusive randomizations. Patients who attain only a PR or SD after 2 cycles of ABVE-PC, the "SERs", will be randomized to +/- DECAx2. This will be followed by 2 additional cycles of ABVE-PC. Patients who attain a CR or VGPR after 2 cycles of ABVE-PC, the "RERs", will proceed to receive 2 more cycles of ABVE-PC before having their response assessed again. If at that time they are a CR, they will be randomized to +/- IFRT. RER patients with VGPR, PR, or SD after 4 cycles of ABVE-PC will be assigned to IFRT. If patients have PD at any time, they are to be taken off protocol therapy per Section 11 of the protocol and followed.

The RDE screen for "**Call-back #1 for Randomized Treatment Assignment**" is to be submitted by the institution for all patients, but **Call-back #2 for Randomized Treatment Assignment**" is only to be submitted for RER patients.

The decision tree below shows the procedure to be followed, including the definitions of RER and SER. See Section 10.0 of the protocol for complete definitions of response criteria.

At Registration:

- All eligible patients are assigned to receive 2 cycles of ABVE-PC induction therapy.

After completion of 2 cycles of ABVE-PC

- Assess the patient's response to induction.
- Submit all scans and worksheets obtained at diagnosis and between Day 15 and 18 of the 2nd ABVE-PC cycle to QARC
- Obtain QARC Central Review and await their response
- Based on QARC review, go to the RDE and complete/submit "**Call-back #1 for Randomized Treatment Assignment**".
- If the patient's response to 2 cycles of induction is:

1) <u>CR or VGPR</u> (then the patient is an RER)
   A) Continue treatment per section 5.2 of the protocol, i.e., 2 more cycles of ABVE-PC. Treatment assignment will occur after this cycle.
   B) After completion of a total of 4 cycles of ABVE-PC:
      1. Assess the RER patient's response to 4 cycles of ABVE-PC.
      2. Send all scans and worksheets after completion of 4 cycles of ABVE-PC to QARC.
      3. ***For only the RER patients***, go to "**Call-back #2 for Randomized Treatment Assignment**" if the patient's response is:
         a) CR; <u>ACTION:</u> RDE randomizes the patient to +/- IFRT.
         b) VGPR, PR, or SD; <u>ACTION</u>: RDE assigns the patient to +IFRT.
         c) PD; <u>ACTION:</u> Take patient off protocol therapy per section 11.0 of the protocol and follow the patient.
2) <u>PR or SD</u> (then the patient is an SER)
   A) RDE randomizes the patient to +/- DECAx2. All then get two additional cycles of ABVE-PC. Treat patient per section 5.3 of the protocol.
      - Send all scans obtained prior to, during, and at the end of chemotherapy; as well as radiation planning films to QARC prior to start of radiotherapy.
3) <u>PD</u> (then the patient has progressive disease)
   A) Take patient off protocol therapy per section 11.0 of the protocol and follow the patient.

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use 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 the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be filed with the COG Group Operations Center's Regulatory Compliance Office before a patient may be registered on this study.

**SAMPLE INFORMED CONSENT DOCUMENT**

**AHOD0031**, *A Phase III Group-wide Study of Dose-intensive Response-based Chemotherapy and Radiation Therapy for Children and Adolescents with Newly Diagnosed Intermediate Risk Hodgkin Disease*

**WHAT IS THIS STUDY ABOUT?**
This study is a clinical trial (a research study involving human patients). Clinical trials only include patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

This study is being carried out by the Children's Oncology Group (COG). COG is an international research group that consists of more than 200 hospitals in the United States, Canada, Australia, New Zealand, the Netherlands and Switzerland that treat children with cancer. It is common medical practice to treat children with cancer on international research studies like this one.

You are being asked (to allow your child) to take part in this study because you (your child) has a type of cancer called Hodgkin disease, a cancer of the lymph system. The lymph system is made up of tissue throughout the body that makes and stores infection-fighting cells. Hodgkin disease is one of the most treatable childhood cancers. The standard treatment for Hodgkin disease involves chemotherapy (treatment with anti-cancer drugs) and radiation therapy (the use of high-dose x-rays to kill cancer cells). Although they are cured from their cancer, some patients experience negative effects from treatment later in life. These kinds of side effects are often referred to as late effects. This can include problems with growth, problems with some organ functions, and sometimes second cancers. These types of effects can be associated with either chemotherapy or radiation therapy. We are therefore designing studies to minimize or prevent these late effects. It is thought that if some patients can be successfully treated without radiation, those patients might experience fewer late effects.

This clinical trial looks at whether some patients, who respond very well to treatment early on (rapid early responders), can be given treatment that does not include radiation without losing any treatment benefit. To accomplish this, some rapid early responders will be given treatment without radiation therapy while others will be given standard treatment (which includes radiation therapy). The treatment arm that does **not** include radiation therapy is considered an **experimental** arm of treatment.

Some patients, however, do not respond as well to the first stages of treatment (slow early responders). Slow early responders are considered to be at higher risk for relapse. This study also looks at whether these kinds of patients will benefit from additional chemotherapy. To accomplish this, some slow early responders will be given treatment with additional chemotherapy while others will be given standard treatment (which includes the standard

amount of chemotherapy). The treatment arm with additional chemotherapy is considered an **experimental** arm of treatment.

**WHY IS THIS STUDY BEING DONE?**
**We are hoping to learn whether we can modify treatment based on early response in a way that reduces therapy for rapid early responders and increases therapy (and hopefully outcome) in slow early responders. In particular, the goals of the study are:**

- **To find out if more therapy for slow early responders is better than the standard therapy;**
- **To find out if patients who have an early complete response to chemotherapy can be treated successfully without radiation therapy;**
- **To find out if certain factors like symptoms, age, sex, and blood test results predict how well a patient will respond to treatment;**
- **To find out which late effects occur after Hodgkin disease treatment and how often they occur; and**
- **To collect information on how PET scans* provide useful information about which places in the body are affected by Hodgkin Disease in children and teenagers.**

** A PET scan is a special kind of test that helps to determine the activity of tumor in the body. It takes about 3-4 hours and involves injecting a small amount of radioactive compound and seeing how much of it collects within the areas of the Hodgkin Disease. It may be easier and more accurate than the gallium scan test that we use now. Not all hospitals will participate in this study of PET scans. Your (your child's) doctor will tell you if your child will get a PET scan, a gallium scan or both tests.*

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**
There will be about 1,700 patients participating in this study.

**WHAT WILL HAPPEN TO ME (MY CHILD) ON THIS STUDY?**

Methods for Giving Drugs
Various methods will be used to give the drugs. Some drugs will be given by tablet or liquid through the mouth. Some drugs will be given using a needle inserted under the skin. Other drugs will be given using a needle inserted into a vein or central line.

Central Line
For drugs to be given by vein, your doctor will likely recommend that you (your child) have a central venous line placed. A central line is a special type of tubing inserted into a large vein in the chest by a surgeon during a short operation. You (your child) would be anesthetized for this procedure and receive pain medication afterwards to keep you (your child) comfortable. The central line is used to administer chemotherapy drugs and to withdraw small amounts of blood for testing during treatment. The risks associated with central lines will be explained to you and all of your questions will be answered. If you are (your child is) to have a central line inserted, you will be given a separate informed consent document to read and sign.

*Randomization*
*Randomization means that the treatment to which a patient is assigned is based on chance. It is like a flip of a coin, and randomization is done by a computer. Neither the patient nor the researcher chooses which group a patient will be in. A patient has an equal chance to be placed in either group. The reason for randomly assigning patients to one of these two treatments is*

*that investigators do not know which treatment will be better for patients with intermediate risk Hodgkin Disease.*

You are (your child is) being asked to agree to be randomized to either standard therapy or experimental therapy.

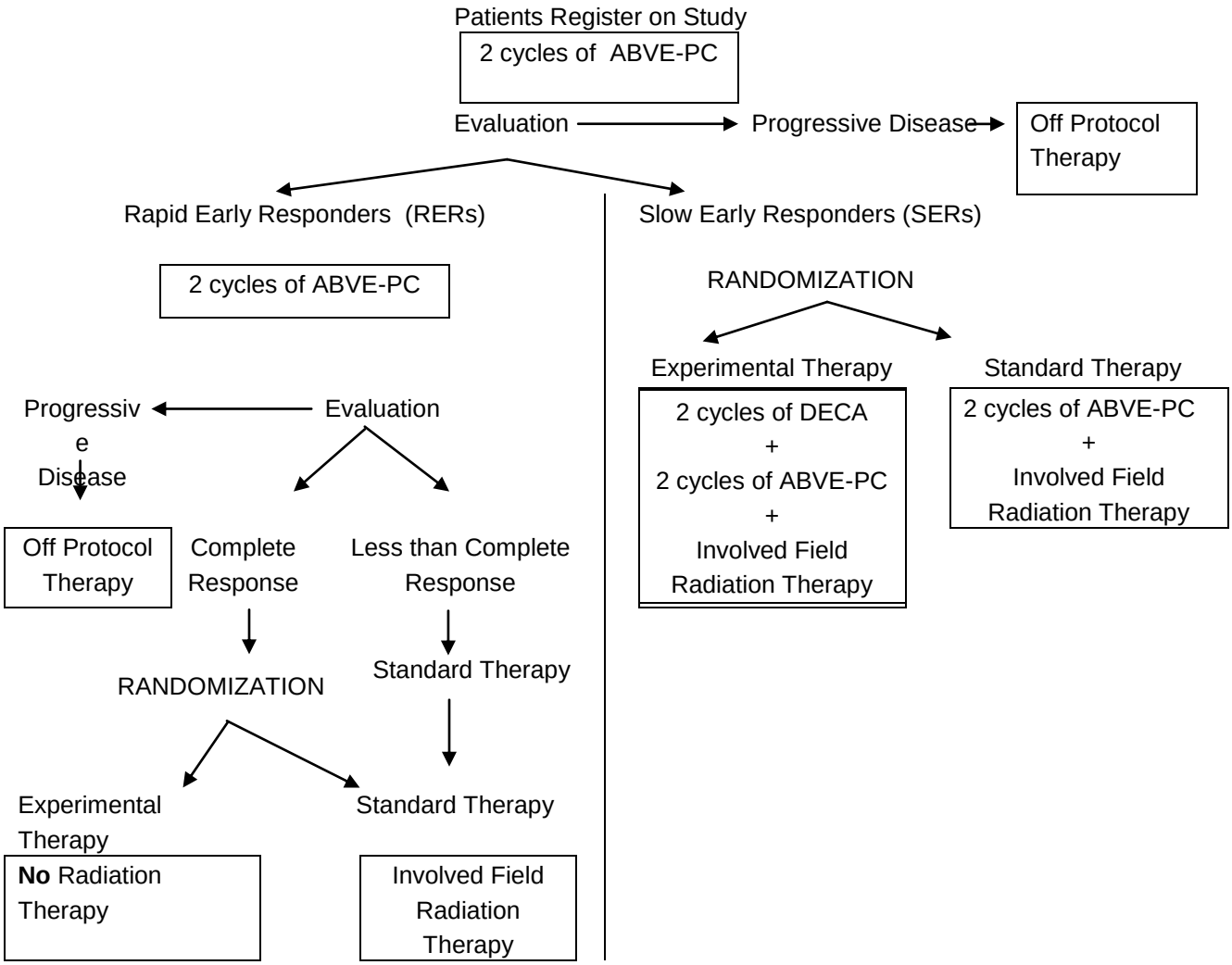
If randomization to either standard or response-based therapy is accepted, you (your child) will be enrolled on this study.

All patients begin treatment on this study with two 21-day cycles of ABVE-PC chemotherapy (an outline of ABVE-PC chemotherapy is provided below). Patients will then be evaluated for their response to treatment. Patients with disease reduction less than 60% are put in the group of Slow Early Responders (SERs). The next step for patients who are SERs is determined by *randomization* to either receive 2 cycles of DECA chemotherapy (an outline of DECA chemotherapy is provided below) plus 2 cycles of ABVE-PC chemotherapy or 2 cycles of ABVE-PC chemotherapy only.

Patients who are SERs then complete treatment with radiation therapy to areas of the body affected by the cancer. Radiation therapy is given 5 days a week (Monday – Friday). The number of treatments will depend on what parts of your (your child's) body requires radiation treatments.

Those patients evaluated as having an early response to treatment will be put in the group of Rapid Early Responders (RERs). The RER group includes those patients whose disease has been reduced by 60% or more. The next step for patients with RERs is 2 more cycles of ABVE-PC chemotherapy followed by another evaluation of their response. Those determined to have a complete response (at least an 80% disease reduction) will be randomized to receive radiation therapy to areas of the body effected by the cancer (Standard therapy arm) or to receive no radiation therapy (Reduced therapy arm). Those patients determined to have less than a complete response, will not be randomized and will automatically be assigned to receive radiation therapy.

An outline of treatment is provided below followed by outlines of the two chemotherapy combinations given on this study.


Patients Register on Study
2 cycles of ABVE-PC
Evaluation
Progressive Disease
Off Protocol Therapy
Rapid Early Responders (RERs)
Slow Early Responders (SERs)
2 cycles of ABVE-PC
RANDOMIZATION
Experimental Therapy
Standard Therapy
2 cycles of DECA
+
2 cycles of ABVE-PC
+
Involved Field Radiation Therapy
2 cycles of ABVE-PC
+
Involved Field Radiation Therapy
Progressive Disease
Evaluation
Off Protocol Therapy
Complete Response
Less than Complete Response
RANDOMIZATION
Standard Therapy
Experimental Therapy
Standard Therapy
No Radiation Therapy
Involved Field Radiation Therapy

**ABVE-PC CHEMOTHERAPY**

| ***Drug*** | ***Method*** | ***Schedule*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | ***Day*** | ***1*** | ***2*** | ***3*** | ***4*** | ***7*** | ***8*** | ***21*** |
| Doxorubicin | By needle inserted into vein (or central line) for 10 to 30 minutes | | X | X | | | | | |
| Bleomycin | By needle inserted into vein (or central line) for 10-20 minutes or inserted beneath the skin | | X | | | | | X | |
| Vincristine | By needle inserted into vein or central line for 5 minutes | | X | | | | | X | |
| Etoposide | By needle inserted into vein or central line for 1 hour | | X | X | X | | | | |
| Prednisone | By mouth (2 or 3 times daily) | | X | → | → | → | → | | |
| Cyclophosphamide | By needle inserted into vein or central line over 1 hour | | X | | | | | | |
| GCSF* | By injection under the skin (1 injection daily, starting day 4) but not on day 8 | | | | | X | → | | → |

*Daily injections of G-CSF will continue until blood tests show that a patient's cell count is adequate.

**DECA**

| ***Drug*** | ***Method*** | ***Schedule*** | | | | |
|---|---|---|---|---|---|---|
| | | ***Day*** | ***1*** | ***2*** | ***3*** | ***21*** |
| Dexamethasone | By needle inserted into vein (or central line) for 15 minutes | | X | X | | |
| Dexamethasone eye solution | 2 drops in each eye every 6 hours | | X | X | X | |
| Etoposide | By needle inserted into vein (or central line) for 3 hours | | X | X | | |
| Cytarabine | By needle inserted into vein (or central line) for 3 hours | | X | X | | |
| Cisplatin | By needle inserted into vein (or central line) for 6 hours | | X | | | |
| GCSF* | By injection under the skin (1 injection daily starting on Day 3) | | | | X | → |

*Daily injections of G-CSF will continue until blood tests show that a patient's cell count is adequate.

Standard Medical Tests

Before treatment on this study begins, and while receiving treatment, you will receive a series of standard medical tests. They may include:

- Physical exams
- Blood tests
- Urine tests
- Tests of bone marrow (the soft tissue in the hollow of flat bones of the body that produces new blood cells)
- *Biopsy of cancerous tissue
- *Pregnancy test**
- *Sperm analysis and banking***
- Various scans
- Tests of thyroid function
- Tests of lung and heart function
- Hearing tests
- Tests of kidney function

*Prior to treatment.
**Given to females of childbearing age prior to treatment.
***For males that have reached puberty.

Following treatment, many of the medical tests listed above will be done every 3 months for the first few 2 years after treatment, every 6 months for 3-5 years following treatment, and every year thereafter. These post-treatment tests are done to test for a return of the cancer and late effects of the treatment.

**Optional Biology Studies**

You (your child) are also being to participate in a biology part of this study. Participating in the biology part of the study is optional. You (your child) will still be on this treatment even if you answer (your child answers) no to any of the questions below.

These research tests will not affect the treatment you receive (your child receives) on this study and therefore the results of these tests will not become part of your (child's) health records, and will not be available to you or your (child's) doctor.

We would like to collect additional blood from you (your child) to see how your (child's) body responds to treatment for Hodgkin Disease. The amount of blood collected will depend on how big you are (your child is). The blood draw will happen at a time when you (your child) is already having blood drawn for routine tests as part of standard care. If you agree, there will be up to five blood draws during months of treatment and one blood draw after treatment. Each blood draw, no more than 60 ml (4 tablespoons), will be taken at diagnosis, at day 7 of the first cycle, after the second cycle , at the completion of the second cycle of DECA for SER patients, at the completion of radiotherapy and 1 year after treatment. This will be a total of no more than 360 ml (24 tablespoons).

If you give permission to use your (child's) samples and later decide that you no longer want your (child's) samples used for these studies, you can let your (your child's) doctor know and the specimens will be destroyed.

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No" then add your initials and date after your answer. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number included in this consent.

1. Additional blood may be taken from me (my child) to be used for the research described above.

#1: YES NO _____
initials and date

If you will allow us, we would also like to use some of your (child's) tumor tissue leftover from your (child's) diagnostic procedure so that we may understand more about Hodgkin disease. We want to learn how therapy affects your (your child's) DNA, which is the genetic material that is in all cells of the body.

2. My (child's) tissue may be kept for use in research to learn about, prevent, or treat cancer.

#2: YES NO _____
initials and date

3. My (child's) tissue may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

#3: YES NO _____
initials and date

<u>After Therapy Ends</u>
After you complete (your child completes) their treatment, they will be followed for at least 10 years to monitor for both relapse (the cancer coming back) or any late effects of treatment. We would like you (your child) to help us understand the effects of therapy by completing a short questionnaire at the end of therapy, and at 1, 3, 5, 7, and 10 years off therapy. This questionnaire will take about 20 minutes to complete. Since patients may move during this period of time, we would also like to contact you (your child) directly during this period of time to provide information about Hodgkin disease, this study and possible other research studies that you (your child) may wish to participate in.

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No" then add your initials and date after your answer. **No matter what you (your child) decide to do, it will not affect your (child's) care.** If you (your child) have any questions, please talk to your (child's) doctor or nurse, or call our research review board at IRB's phone number included in this consent.

I agree to take part in the questionnaire described above.

YES NO _____
initials and date

I agree to provide identifying information to the Children's Oncology Group.

YES NO _____
initials and date

If yes, your doctor will forward to the Children's Oncology Group, your address and telephone number and e-mail address. Each year, the investigators will ask you to update that information, so that we have the most up to date information for you.

In addition, I agree to be contacted directly in the future with information regarding Hodgkin Disease, this study or other studies that may be of interest to me (my child).

YES NO _____
initials and date

**HOW LONG WILL I (MY CHILD) BE ON THIS STUDY?**
You (your child) will be treated on this study for about 4-6 months. However, patients will continue to have medical tests for 10 or more years after treatment so that researchers can continue to observe for signs of relapse (the cancer coming back) or any effects of treatment. In addition, we would like to continue to collect some information about how you are (your child is) doing for about ten years after the last patient starts on the study. Keeping in touch with you and checking on how your health is every year for a while after the study closes helps us understand the long-term effects of the study. (If you (your child) agreed to take part in the late effects 7.1questionnaire, then you (your child) will be on the study for longer than 10 years as explained earlier in the consent).

The researchers may decide to take you (your child) off the study if your (your child's) cancer gets worse or you (your child) experiences side effects from the treatment that are considered too severe.

You can leave (remove your child from) the study at any time. However, if you consider leaving (removing your child from) the study, we encourage you to talk to your (your child's) regular physician and to the research physician before making a final decision. They will help you (your child) stop safely.

**WHAT ARE THE RISKS OF THE STUDY?**
While on the study, you are (your child is) at risk for these side effects. You should discuss these with the researcher and/or your (child's) regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the chemotherapy and radiation therapy are stopped, but in some cases side effects can be serious or long-lasting or permanent.

However, there may be additional risks related to whether you (your child) receive (receives) standard or experimental therapy. Those who are rapid early responders may be more likely to relapse because they do not receive radiation therapy. Those who are slow early responders may have more side effects if they receive the extra DECA chemotherapy. The possible side effects of dexamethasone, etoposide, cisplatin and cytarabine are listed below.

**Chemotherapy agents are drugs that, in addition to killing tumor cells, can damage normal tissue. These drugs, however, have been in use long enough so that severe problems can usually be avoided. Side effects are usually reversible when medication is stopped but occasionally can persist and cause serious complications. The common side effects from cancer treatment include nausea, vomiting and hair loss. Drugs may be given to prevent or counteract nausea and vomiting but sometimes these symptoms may be severe enough that you (your child) will need to have fluid given directly into the vein to replace the fluid loss. Hair loss is usually temporary but on rare occasions it may be permanent. In this study, prolonged depression of the number of blood cells, skin rashes and sores in the mouth and intestines are anticipated. The more serious side effect from cancer treatment is depression of the number of blood cells resulting in anemia, increased chance of infection and bleeding tendency. These complications can sometimes be fatal.**

**If needed, tests will be done to monitor your (your child's) progress and they can include tests like bone marrow aspirates, biopsies, blood work and laboratory tests. In addition, when chemotherapy drugs are combined the side effects can be increased. Finally, a few patients who survive Hodgkin Disease develop a second form of cancer.**

**The following kinds of side effects may be observed from the drugs used in this protocol:**
**Risks and side effects related to Bleomycin include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Chills and a high fever<br>• Darkening of the skin which may be associated with itching and scratching<br>• Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (painful mouth sores)<br>• Blanching (whiteness) of the fingers or toes when they are exposed to cold or when you are under stress, that may make them feel cold or throb and ache | • Rashes which may be located in pressure points where the clothes contact the body or thickening of the skin<br>• Changes in taste and loss of appetite<br>• Weight loss<br>• Inflammation of the lungs that can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood making you short of breath<br>• Shortness of breath with or without a wet crackly noise in your chest<br>• Nausea and/or vomiting<br>• Temporary loss of hair<br>• Pain and inflammation in the vein through which the drug was given<br>• A feeling of extreme tiredness, weakness or not feeling well<br>• The finger or toe nails may loosen from their nail beds or the nails may thicken or darken at the cuticle<br>• Fewer platelets in the blood (a low number of platelets causes you to bruise and bleed more easily) | • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever<br>• Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath<br>• Damage and scarring of the lungs that can lead to fluid in the lungs and affect your ability to breath and the levels of oxygen in your blood which has rarely led to death<br>• In combination with other chemotherapy drugs, Bleomycin has very rarely been associated with severe cardiovascular events such as heart attack or stroke. This is more likely to occur in patients who are older. |

**Risks and side effects related to cisplatin include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Nausea and vomiting<br>• fewer red blood cells and white blood cells and platelets in the blood<br>  ○ a low number of red blood cells can make you feel tired and weak<br>  ○ a low number of white blood cells can make it easier to get infections<br>  ○ a low number of platelets causes you to bruise and bleed more easily<br>• Abnormal levels of magnesium in the body which may require that you take extra magnesium by mouth or in the vein<br>• Loss of appetite<br>• Damage to the ear causing difficulty in hearing high pitched sounds<br>• Temporary and mild increases in levels of certain chemicals in the blood because the kidney is not working as well as normal | • Abnormal levels of certain salts in the body like sodium, calcium, potassium and phosphate<br>• Metallic taste<br>• Rash<br>• Numbness and tingling in the fingers and toes<br>• Temporary changes in vision<br>• Damage to the ear causing hearing loss, balance problems and ringing in the ears<br>• Elevation in the blood of certain enzymes found in the liver<br>• Inflammation and discomfort in the vein through which the medicine was given | • Allergic reactions which may be severe and life-threatening, causing difficulty in breathing, rapid heart rate, facial swelling and or a drop in blood pressure<br>• Damage to the kidney which may be permanent<br>• Deafness<br>• Seizures<br>• Damage to the vision which could lead to blurred vision, blue-green color blindness and to loss of vision which usually goes away after stopping the drug.<br>• Decrease in muscle and nerve reflexes that may affect normal functions such as walking<br>• Leukemia later in life |

**Risks and side effects related to cyclophosphamide include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Loss of appetite<br>• Nausea<br>• Vomiting<br>• Fewer white blood cells in the blood.<br>  ○ A low number of white blood cells may make it easier to get infections.<br>• Hair loss<br>• Decreased ability of the body to fight infection<br>• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children | • Abnormal hormone function which may lower the level of salt in the blood<br>• Abdominal pain<br>• Diarrhea<br>• Fewer red blood cells and platelets in the blood<br>  ○ A low number of red blood cells may make you feel tired and weak.<br>  ○ A low number of platelets may cause you to bruise and bleed more easily.<br>• Bleeding and inflammation of the urinary bladder<br>• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children<br>• Temporary blurred vision<br>• Nasal stuffiness with IV infusions<br>• Skin rash<br>• Darkening of areas of the skin and finger nails<br>• Slow healing of wounds<br>• Infections | • Heart muscle damage which may occur with very high doses and which may be fatal<br>• Abnormal heart rhythms<br>• Damage and scarring of lung tissue which may make you short of breath<br>• A new cancer or leukemia resulting from this treatment.<br>• Damage or scarring of urinary bladder tissue<br>• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever<br>• Infertility which is the inability to have children |

**Risks and side effects related to cytarabine include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Nausea and vomiting<br>• Hair loss<br>• Mouth sores<br>• Loss of desire to eat<br>• Fewer red and white blood cells and platelets in the blood<br>  ○ a low number of red blood cells can make you feel tired and weak<br>  ○ a low number of white blood cells can make it easier to get infections<br>  ○ a low number of platelets causes you to bruise and bleed more easily<br>• Redness, pain and inflammation of the eye with higher doses | • Rash<br>• Severe rash with redness and pain on the palms of the hand and soles of the feet<br>• Flu type symptoms with fever, tiredness, aches and pains<br>• Diarrhea<br>• Low levels of certain salts in the body like potassium and calcium<br>• Difficulty emptying the bladder<br>• High levels of uric acid in the blood which could damage the kidneys<br>• With higher doses of cytarabine fluid may accumulate in the lungs making it difficult to breathe | • Allergic reactions (can be severe and life-threatening causing difficulty in breathing and or a drop in blood pressure)<br>• A syndrome called Ara-C syndrome where there is fever, aches, pains, sometimes chest pain, a rash and inflammation of the eye<br>• With higher doses of cytarabine there can be effects on the brain which can lead to headaches, incoordination of the muscles when walking, rapid jerky eye movements, difficulty with speech, sleepiness, personality changes, coma<br>• With higher does of cytarabine there can be effects on the heart which can lead to chest pain and damage to the heart muscle<br>• 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.<br>• Kidney Damage<br>• Muscle breakdown which can lead to injury to the kidneys and other organs |

**Risks and side effects related to dexamethasone include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Overeating<br>• Difficulty sleeping or falling asleep<br>• Decreased ability of the body to fight infection<br>• Personality changes with mood swings<br>• Changes in hormone production that cause weight gain especially around the abdomen and shoulders, puffy cheeks, muscle weakness and make your body less able to deal with stress<br>• Pimples | • Red face<br>• Fluid retention<br>• Wounds don't heal as well<br>• Slowed growth<br>• Upset and irritated stomach with heartburn<br>• Stomach ulcers<br>• High blood sugar which may require treatment<br>• Stretch marks and easy bruising of the skin<br>• Abnormal amounts of uric acid in the blood<br>• Increased pressure in the eyes<br>• High blood pressure<br>• Lessening of calcium in the bones making them more susceptible to fracture<br>• Cataracts which are usually more reversible in children<br>• Headache<br>• dizziness | • Damage to the joints which can result in pain and loss of motion usually involving the joints of the hip and knee<br>• Inflammation of the pancreas<br>• Stomach and intestinal tract bleeding from ulcers<br>• Infections<br>• Increased pressure in the brain which can lead to difficulty seeing, pressure in the eyes and headache<br>• Bone Fractures<br>• Serious changes in mood, personality and/or severe depression |

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

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Nausea<br>• Vomiting<br>• Temporary hair loss<br>• Pink or red color to urine, sweat, tears, saliva<br>• Fewer white blood cells, red blood cells and platelets in the blood.<br>  ○ A low number of red blood cells can make you feel tired and weak<br>  ○ A low number of white blood cells can make it easier to get infections<br>  ○ A low number of platelets causes you to bruise and bleed more easily<br>• Slight damage to the heart muscle that is unlikely to have any noticeable effects on your heart function | • 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)<br>• Damage to the heart muscle which may make you tired, weak, feel short of breath, and retain fluid<br>• Facial Flushing<br>• Fever/chills<br>• Hives<br>• High levels of uric acid in the blood which could damage the kidneys<br>• Dark discoloration of the hands, feet and under the fingernails with possible separation of the nail from the nail bed.<br>• Damage to the skin if the medication leaks from a vein<br>• Thickening and hardening of the veins through which the medication is given<br>• Reddening reaction of the vein when through which the drug is given.<br>• Elevation in the blood of certain enzymes found in the liver<br>• Tearing and inflammation of the eyes<br>• Loss of appetite<br>• Redness and burning at sites which have received radiation in the past<br>• Diarrhea | • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate<br>• Ulceration of the lower intestinal tract<br>• An irregular heart beat which can be life-threatening<br>• Severe damage to the heart muscle which may lead to severe heart failure<br>• A new cancer or leukemia resulting from this treatment. |

**Risks and side effects related to etoposide include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Nausea and vomiting<br>• Hair Loss<br>• A feeling of weakness or tiredness<br>• fewer red and white blood cells and platelets in the blood<br>  ○ a low number of red blood cells can make you feel tired and weak<br>  ○ a low number of white blood cells can make it easier to get infections<br>  ○ a low number of platelets causes you to bruise and bleed more easily | • Loss of appetite<br>• Decreased blood pressure during the infusion which may require treatment<br>• rashes<br>• Diarrhea<br>• Pain in the abdomen<br>• Mouth sores<br>• Tingling sensation or loss of sensation in fingers or toes<br>• A feeling of extreme tiredness or weakness<br>• The finger or toe nails may loosen from their nail beds<br>• Inflammation of the vein through which the medication was given<br>• Chest pain | • Damage to the liver<br>• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever<br>• A new cancer or leukemia resulting from this treatment<br>• Severe rashes which can result in loss of skin and damage to mucous membranes<br>• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children<br>• Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid |

## Risks and side effects related to Filgrastim (G-CSF) include those which are:

**Risks and side effects related to Filgrastim (G-CSF) include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Aching or pain in the bones | • Local irritation at the site of the injection<br>• Headache<br>• Higher than normal levels of liver enzymes which may indicate liver irritation or damage and uric acid in the blood<br>• A low number of platelets in the blood which may cause you to bruise and bleed more easily<br>• Low fever<br>• Enlargement of the spleen which may cause pain in the abdomen or left shoulder<br>• Worsening of skin rashes<br>• Inflammation of a blood vessel in the skin leading to a raised purple rash and bruising<br>• Higher than normal white blood count | • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives and facial swelling. This reaction is very rare and has been associated mainly with intravenous administration.<br>• If you are known to have sickle cell disease, filgrastim may cause a sickle cell crisis.<br>• Severe damage to the spleen (an organ in the abdomen/belly which stores blood cells) which could lead to pain and loss of blood into the abdomen (belly) and maybe life threatening<br>• Difficulty breathing and lung damage that may be due to the white blood cells that are stimulated by filgrastim traveling to the lungs when they are inflamed or infected.<br>• A blood disorder or leukemia that has only been seen in patients with certain immune disorders who are treated for a very long time. |

**Risks and side effects related to Prednisone include those which are:**

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Overeating<br>• Difficulty sleeping or falling asleep<br>• Decreased ability of the body to fight infection<br>• Personality changes with mood swings<br>• Changes in hormone production that cause weight gain especially around the abdomen and shoulders, puffy cheeks, muscle weakness and make your body less able to deal with stress<br>• Pimples | • Red face<br>• Fluid retention<br>• Wounds don't heal as well<br>• Slowed growth<br>• Upset and irritated stomach with heartburn<br>• Stomach ulcers<br>• High blood sugar which may require treatment<br>• Stretch marks and easy bruising of the skin<br>• Abnormal amounts of salts and uric acid in the blood<br>• Increased pressure in the eyes<br>• High blood pressure<br>• Lessening of calcium in the bones making them more susceptible to fracture<br>• Cataracts which are usually more reversible in children<br>• Headache<br>• dizziness | • Damage to the joints which can result in pain and loss of motion usually involving the joints of the hip and knee<br>• Inflammation of the pancreas<br>• Stomach and intestinal tract bleeding from ulcers<br>• Infections<br>• Increased pressure in the brain which can lead to difficulty seeing, pressure in the eyes and headache<br>• Bone Fractures<br>• Serious changes in mood, personality and/or severe depression |

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

| Likely | Less Likely | Rare but serious |
|---|---|---|
| • Hair loss<br>• Reversible nerve problem that may affect the way you walk or the feelings in your fingers or toes<br>• Constipation | • Jaw pain<br>• Headache<br>• Muscle Weakness<br>• Pain and bloating in your abdomen<br>• Numbness and tingling<br>• Wrist or foot drop<br>• Drooping eyelids<br>• Double vision, difficulty seeing at night<br>• Abnormal walk with foot slapping<br>• Difficulty with urination or increase desire to urinate<br>• Dizziness<br>• Abnormal hormone function which may lower the level of salt in the blood<br>• Seizures<br>• A mild drop in white blood cells, red blood cells and platelets in the blood<br>○ a low number of red blood cells can make you feel tired and weak<br>○ a low number of white blood cells can make it easier to get infections<br>○ a low number of platelets causes you to bruise and bleed more easily | • Complete stoppage of your intestinal activity which can result in intestinal blockage<br>• If the drug leaks out of the vein when being administered it will cause damage to nearby tissue<br>• Seizures<br>• Vocal cord paralysis<br>• Difficulty breathing<br>• Inability to walk<br>Decreased ability to hear clearly<br>• Damage to the nerve to the eye (optic nerve) leading to decreased vision and possible blindness<br>• 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 |

**Potential Risks of Radiation Therapy:**

**It is possible that there may be irritation or damage of any organ that is receiving radiation therapy. The most common organs that could be damaged in the treatment of Hodgkin disease with radiation therapy are the thyroid gland, heart, lungs, liver, spleen, intestines, kidneys and ovaries or testes. Radiation therapy is also associated with an increased risk of second cancers, the most common of which are leukemia, breast and thyroid cancer. All normal organs will be shielded whenever possible to help protect them from damage. If pelvic radiation is required for girls, surgery may be done to move the ovaries out of the radiation field. The most common side effects of radiation therapy for Hodgkin disease are: skin changes that may include irritation, darkening, or a possible burn; mouth ulcers, sore throat, pain on swallowing, nausea, vomiting, diarrhea, generalized weakness and fatigue. If you (your child) receive radiation therapy on this study, you (your child) will meet with a radiation oncologist, who will discuss all of the possible side effects of radiation therapy in detail with you, before the radiation therapy is given.**

**Radiation Risks from the PET, gallium and CT scans:**

**You will get a radiation dose that is eighty times higher than a chest x-ray from a CT or PET scan. The radiation dose from a gallium scan is about the same or a little more than CT or PET scans. The amount of radiation you get from the radioactive tracers used for any of these scans is within the range that doctors think is acceptable for diagnostic testing. The dose you get is about 15% of the yearly exposure level allowed by federal regulations for people who work with radioactive materials.**

**There is no known minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic defects or cancer. There is always a slight risk of damage to cells or tissues from being exposed to any radiation, including the low level of radiation released by the radioactive tracer used for these tests.**

**Most of the radioactive tracer injected to do the scans will be eliminated from your body within 6 to 24 hours. Allergic reactions to tracers are very rare. Sometimes some soreness or swelling may develop where the tracer is injected. There may be pain, bruising and the possibility of infection from the needle stick.**

***The drugs in this study can affect an unborn baby.*** *You (your child) should not become pregnant or father a baby while on this study. You (your child) should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.*

Other presently unknown side effects may be encountered. Your child will be watched closely and the drugs will be discontinued if serious side effects develop.

**WILL MY CHILD BENEFIT FROM THIS STUDY?**
There may or may not be direct medical benefits to you (your child) from taking part in this study. However, if you (your child) are (is) a rapid early responder and do (does) not receive radiation therapy, there may be fewer side effects. If you (your child) are (is) a slow early responder and receive(s) the extra DECA chemotherapy, this may increase the chance for cure.

It is hoped that the information learned from this study may help future patients with Hodgkin disease.

**ARE THERE OTHER TREATMENT OPTIONS?**

**YES, THERE ARE OTHER OPTIONS.**

- **The standard treatment for Hodgkin disease; or**
- **Another experimental treatment (if available).**

Please discuss these options with your regular doctor as well as other trusted personal and family advisors.

**WILL MY (MY CHILD'S) RECORDS BE CONFIDENTIAL?**
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 the certificate is attached at end of this consent.

**Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:**

- **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 keeping research safe for people**
- **The Institutional Review Board (IRB) of this hospital**

**WILL I HAVE TO PAY FOR THIS TREATMENT?**
Taking part in this study may lead to added costs to you or your insurance company. 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 (your child) 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.

You (Your child) will receive no payment or money for taking part in this study. If this study includes providing specimens to the researcher, you (your child) will not profit from any new products developed from research done on your (child's) specimens.

**WHAT ARE MY (MY CHILD'S) RIGHTS AS A STUDY PARTICIPANT?**
Taking part in this study is voluntary. You may choose (for your child) not to participate in this study. If you decide not to (let your child) participate, you (your child) will not be penalized and you (your child) will still receive the standard treatment.

If you choose to (allow your child to) participate, you may discontinue your (your child's) participation in the study at any time. If you discontinue participation in the study, physicians and hospital personnel will still take care of you (your child).

You also have the right to know about new information that may affect your (your child's) health, welfare, or your willingness to (let him/her) participate in the study. You will be provided with this information as soon as it becomes available. 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.

Whether you participate or not, you (your child) will continue to get the best medical care this hospital can provide.

To make communication with you (your child) easier once treatment has ended, we are also asking you (your child) to provide direct contact information. You (your child), may participate in this study without providing this information.

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.

**WHAT IF I HAVE QUESTIONS OR PROBLEMS?**

For questions about the study or a research-related problem , contact Dr. XXXX or your doctor at XXXXX.

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 (XXXX

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 XXXX

**WHERE CAN I GET MORE INFORMATION?**
The **COG 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/

Visit the *NCI's Web site* at http://www.nci.nih.gov/cancerinfo/

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) or TTY: 1-800-332-8615

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

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

## SIGNATURE

I agree to (allow my child to) take part in this study.

Participant_____Date _____

Patients 18 years of age or older are required to sign. Patients age 14-17 are encouraged to be part of the consenting process and may choose to sign the consent.

Parent/Guardian_____Date _____

Parent/Guardian_____Date _____

Physician/PNP obtaining consent_____Date _____
IRB# IRB Approved:

## Attachment
## 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.