National Standard of Care Protocol for Treatment and Management of Retinoblastoma

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1.0 BACKGROUND

1.1 Introduction:

Retinoblastoma (RB) is the most common ocular malignancy in children with an annual incidence of 1;15000-20000 live births.[1] National data regarding incidence of RB in Pakistan is not available but annual crude incidence of RB is 4/100000 in children under 5 years in Karachi, Pakistan.[2] Prognosis in high income countries has improved significantly with overall survival of almost 100% but outcomes in low and middle income countries remain poor due to late presentation.[3] [4] Similar trend is seen in Pakistan with a high proportion of patients presenting with advanced stage disease. [5] Data regarding RB in Pakistan is limited to single institution reviews and there is a need to standardize treatment and study outcomes of RB at a national level in Pakistan. [2,5–7]

The aim is to conduct a national study for the treatment and management of patients diagnosed with Retinoblastoma at multiple institutions across Pakistan. We plan to study the clinical characteristics of all RB patients and assess the effects of a national standardized treatment protocol for unilateral non-metastatic Retinoblastoma.

1.2 Treatment strategy:

The treatment for RB is multimodality including a combination of focal therapy, chemotherapy, surgery and radiation. As treatment depends on extent of disease treatment strategy for this protocol will be divided in two groups based on the International Retinoblastoma Staging System (IRSS).[8] Intra-ocular RB will be further grouped based on International Intraocular Retinoblastoma Classification(IIRC).[9–11]

1.3 Intra-ocular RB (stage 0, I&II)

IIRC is shown to be predictive of effectiveness of chemotherapy in eye salvage with 100%, 93% and 90% eye salvage results reported for group A, B and C eyes. [11] The addition of focal therapy has been shown to improve response. [6] Therefore, our strategy for group A-C will include a combination of focal therapy and systemic chemotherapy. In centers where intra-arterial chemotherapy is available can be used instead of systemic chemotherapy. As probability of eye salvage is only 47% for group D eyes with a 25% chance of relapse in salvaged eye the protocol recommendation will be to proceed with enucleation for group D eyes unless eye salvage is recommended after multidisciplinary team meeting for selected group D eyes with vision. All group E eyes will undergo upfront enucleation with adjuvant chemotherapy based on histology.

Combination chemotherapy including vincristine, etoposide and carboplatin will be used as this has been shown to be effective, well tolerated and easily administered in low and middle income countries. [4,12–14]

Refusal of enucleation is a major reason for treatment abandonment in patients with RB. The outcomes for patients who abandon treatment are poor with survival rates below 50% in those that return later. The use of neo-adjuvant chemotherapy in patients who refuse enucleation has been shown to reduce rates of abandonment in China and South America, however, Zhao et al have shown that outcomes for patients with group E eyes that receive neoadjuvant chemotherapy is inferior and is worse for patients whose enucleation is delayed beyond 3 months from diagnosis. Therefore, up to two cycles of chemotherapy may be offered preoperatively to patients with group E eye to reduce abandonment. These patients with complete total six cycles of chemotherapy as histopathologic risk stratification is not reliable after administration of neoadjuvant chemotherapy.[4,15,16]

1.4 Extra-ocular non-metastatic RB (stage III)

Stage III retinoblastoma is associated with high risk of metastatic disease and relapse. According to the SIOP/PODC guidelines, combination of neoadjuvant chemotherapy, enucleation adjuvant chemotherapy and radiation should be considered for this group. However, a single best chemotherapy regimen is not recommended.[4] Chawla et al conducted a randomized trial comparing two commonly used protocols; carboplatin/etoposide alternating with vincristine/idarubicin/cyclophosphamide compared to vincristine/etoposide/carboplatin. They demonstrated overall survival of 63% at 4 years (compared to 25% for the other group) using a combination of vincristine, etoposide and carboplatin (CEV) at higher doses than that used for intra-ocular RB. This regimen had less toxicity and myelosuppression compared to anthracycline based regimens.[17]

There is concern for *risk of secondary malignant neoplasms* due to the higher dose of etoposide used in this protocol. The association of secondary malignancies has not been consistently associated with cumulative dose of etoposide. Smith et al demonstrated that the risk of development for secondary leukemia and myelodysplastic syndrome was similar in patients receiving low, moderate and high doses of epipodophyllotoxins. The risk of secondary leukemia is higher when etoposide is used in combination with alkylating agents or anthracyclines; so that will be reduced by adopting the CEV protocol. Etoposide will be given over two days as risk for secondary malignancy has been shown to be associated with schedule for administration rather than the cumulative dose in leukemia patients.[18–21]

2.0 STUDY DESIGN, AIMS and OBJECTIVES

2.1 Study Design

This is an observational, non-interventional, standard-of-care and management study that will be prospectively collecting data on patients diagnosed with Retinoblastoma (RB) including unilateral non-metastatic RB, bilateral RB and metastatic RB. Additionally, patients with unilateral, non-metastatic RB will be treated according to a standardized treatment and hospital strategy.

2.2 Aims

Aim of this study is to diagnose, treat and collect information of all children with RB according to a standardized protocol at all institutions across Pakistan, resulting in greater accuracy in diagnosis and improved survival.

2.3 Objectives

2.3.1 Primary Objectives

2.3.1.1 To collect national level data for presentation and clinical features of RB in children in Pakistan.

2.3.1.2 To determine the survival (overall and event-free) of patients with unilateral, non-metastatic RB treated according to a standardized treatment protocol.

2.3.2 Secondary Objectives

2.3.2.1 To determine the geographic, demographic and stage distribution of RB patients in Pakistan.

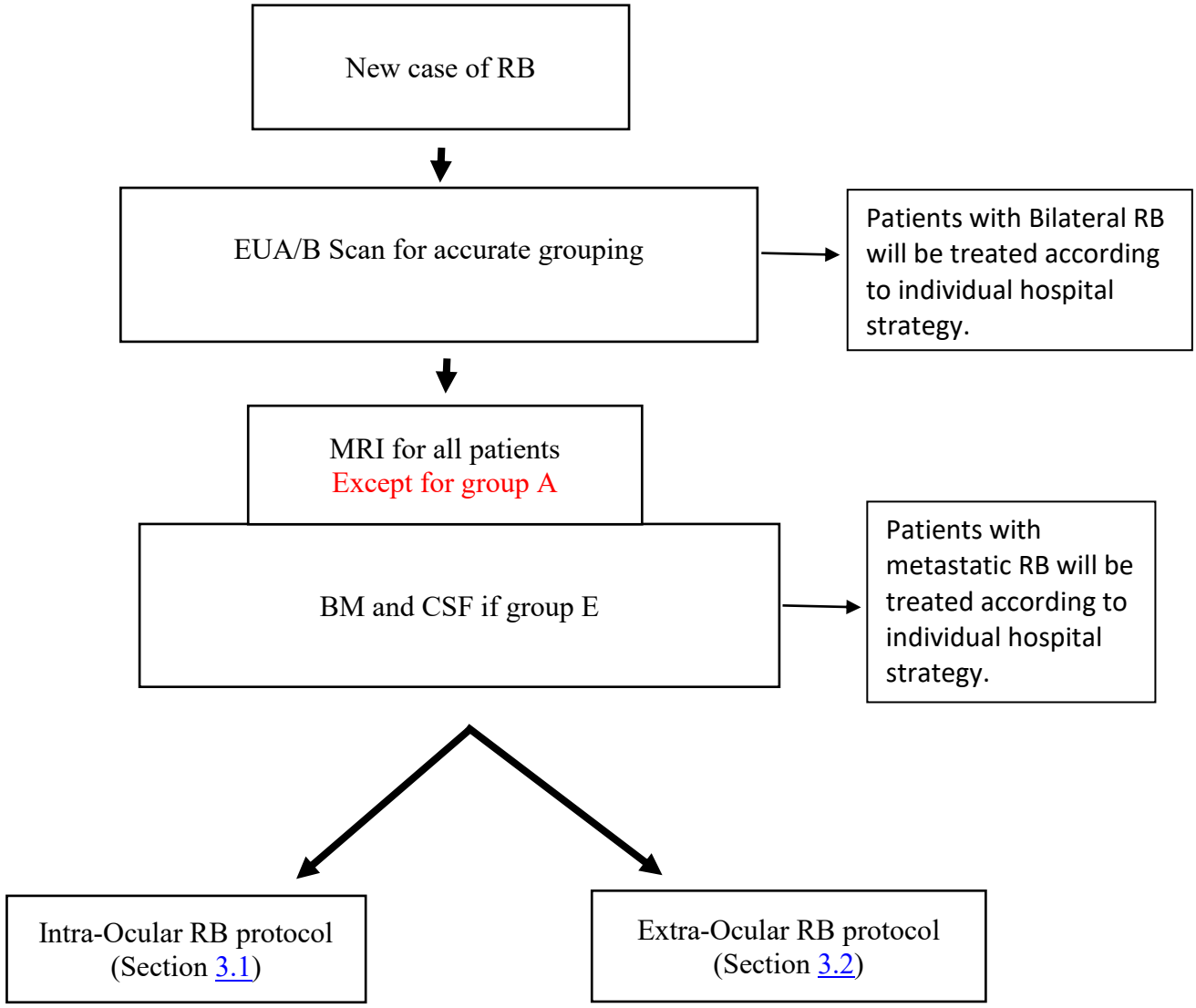
2.3.2.2 To determine the outcome (overall survival and event free survival) based on standardized staging of RB.

2.3.2.3 To determine the ocular survival of patients with unilateral RB based on standardized staging

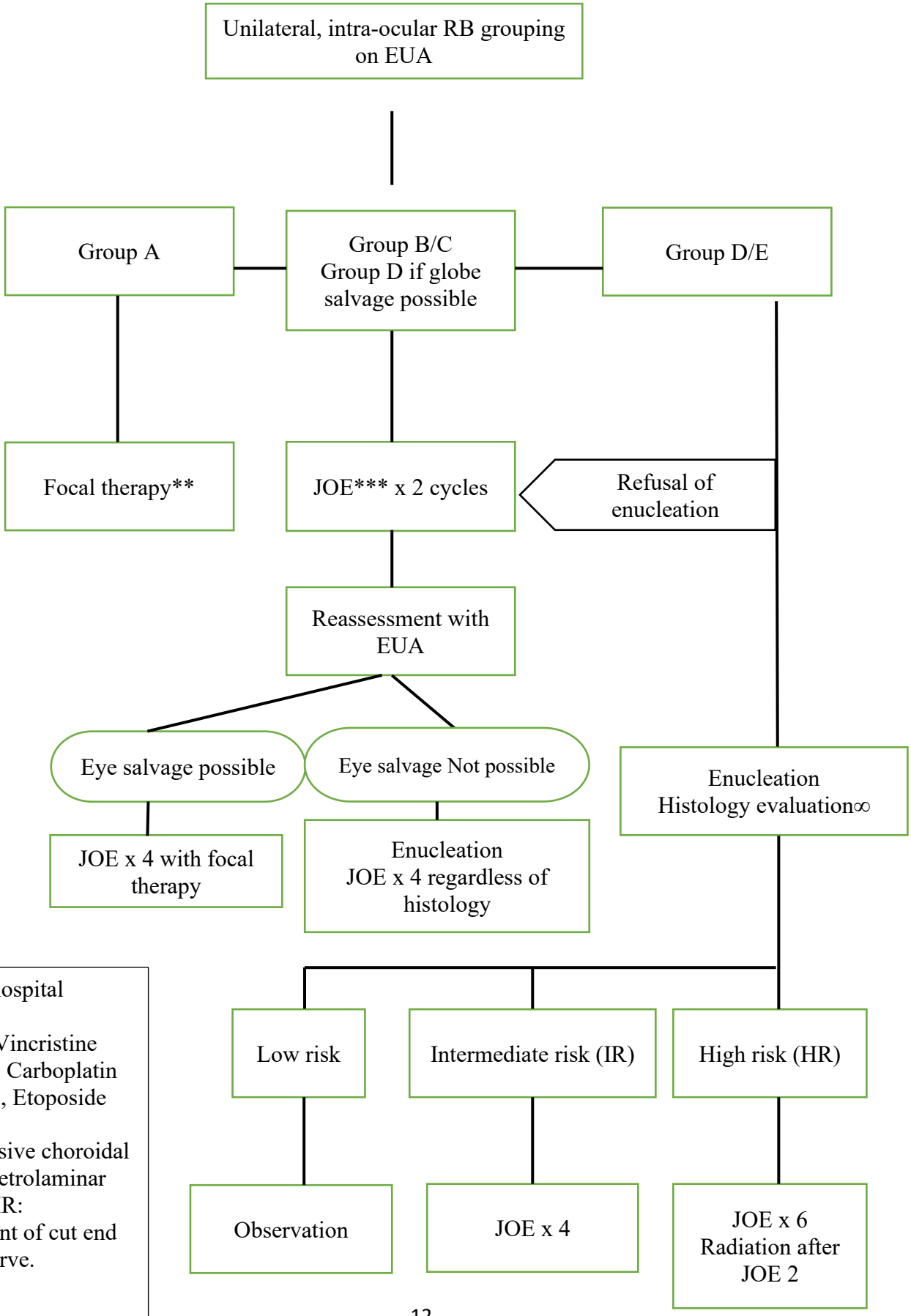
2.3.2.4 To collect data on use and outcome of intra-arterial chemotherapy (AIC) in centers where it is available

2.3.2.5 To estimate the frequency of patients who fail to complete treatment due to abandonment of therapy.

3.0 TREATMENT SCHEMA

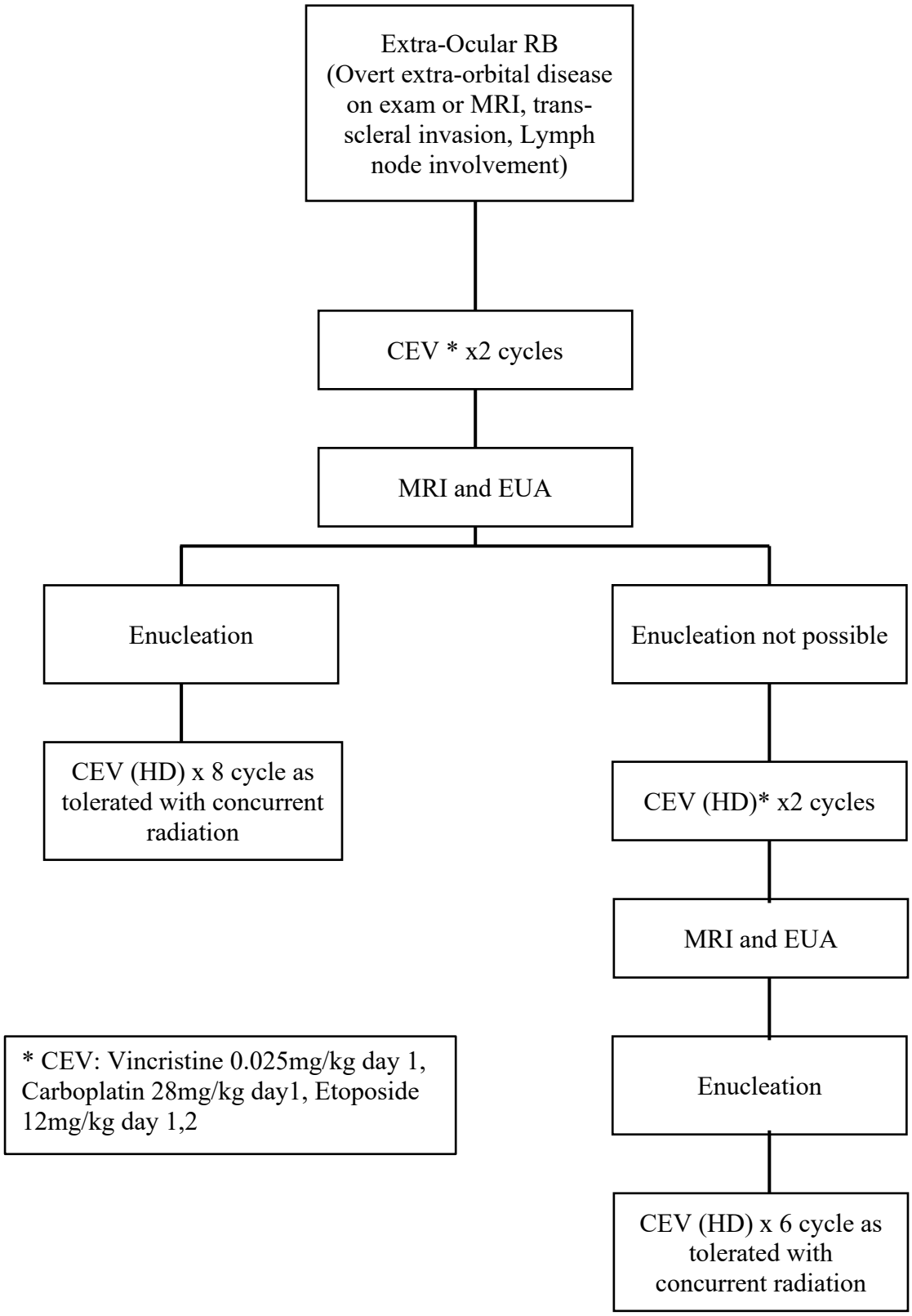


3.1 Intra-ocular RB Protocol



** as per hospital guidelines
*** JOE: Vincristine 1.5mg/m2, Carboplatin 600mg/m2, Etoposide 300mg/m2
∞ IR: Massive choroidal invasion, retrolaminar invasion HR: Involvement of cut end of optic nerve.

3.2 Extra-ocular RB Protocol



4.0 PATIENT ELIGIBILITY AND DEFINITIONS

4.1 Eligibility

4.1.1 Inclusion Criteria

- Diagnosis of Retinoblastoma (RB) confirmed by ophthalmologist on examination under anesthesia (EUA)
- Age ≤18 years at time of enrollment.
- Previously untreated by chemotherapy.
- Patients who have received focal therapy or enucleation at outside institution prior to presentation can be included.
- Informed consent reviewed and signed by the patient, parent or legal guardian.

4.1.2 Exclusion Criteria

- Ocular tumors other than retinoblastoma.

4.2 Definitions

4.2.1 Definition of intra-ocular retinoblastoma (IO RB):

- RB that is confined inside the globe
- No involvement of bone marrow or cerebrospinal fluid by tumour cells
- No intracranial extension on MRI.
- No overt extra-ocular spread on exam e.g proptosis, eye lid involvement, lymph node enlargement etc.
- No evidence of extra-ocular spread on MRI beyond intra-ocular portion of optic nerve. Patients with enhancement of optic nerve without clear involvement may be included after MDT review with radiologist.

4.2.2 Definition of extra-ocular non-metastatic retinoblastoma (EO RB):

- Overt extra-ocular spread on exam e.g. proptosis, eye lid involvement, lymph node enlargement etc.
- presence of spread outside the globe on MRI including involvement of intra-orbital or intra-canalicular portions of optic nerve or trans-scleral extension or involvement of pre-auricular or unilateral cervical lymph nodes.
- No involvement of pre-chiasmatic portion of optic nerve.
- No involvement of bone marrow or cerebrospinal fluid by tumour cells
- No intracranial extension.
- No involvement of optic nerve beyond intra-canalicular portion.
- For patients undergoing enucleation, evidence of extra-ocular spread including trans-scleral extension of tumour can be included.

4.2.3 Definition of groups (A-E) for IO RB

Definitions will be based on IIRC staging system [10]

Group A—very low risk

Eyes with small discrete tumors away from critical structures

All tumors are 3 mm or smaller, confined to the retina, and located at

least 3 mm from the foveola and 1.5 mm from the optic nerve.

No vitreous or subretinal seeding is allowed.

Group B—low risk

Eyes with no vitreous or subretinal seeding and discrete retinal tumor

of any size or location

Retinal tumors may be of any size or location not in Group A.

No vitreous or subretinal seeding allowed. A small cuff of subretinal
fluid extending no more than 5 mm form the base of the tumor is allowed.

Group C—moderate risk

Eyes with only focal vitreous or subretinal seeding and discrete retinal tumors of any size and location

Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Retinal tumors are discrete and of any size and location. Up to one quadrant of subretinal fluid may be present.

Group D—high risk

Eyes with diffuse vitreous or subretinal seeding and/or massive, nondiscrete endophytic or exophytic disease

Eyes with more extensive seeding than Group C.

Massive and/or diffuse intraocular disseminated disease may consist of fine or
‘‘greasy’’ vitreous seeding or avascular masses. Subretinal seeding may be plaque-like. Includes exophytic disease and more than one quadrant of retinal detachment.

Group E—very high risk

Eyes that have been destroyed anatomically or functionally by the tumor

Eyes with one or more of the following:

irreversible neovascular glaucoma, massive intraocular hemorrhage, aseptic orbital cellulitis, tumor anterior to anterior vitreous face, tumor touching the lens, diffuse infiltrating retinoblastoma, phthisis or pre-phthisis

4.2.4 Definition of Histologic risk groups

These definitions will only be applicable to eyes that undergo upfront enucleation. Eye that have received systemic or intra-arterial chemotherapy will be excluded from histologic risk grouping. The risk factor definition will be based on review of 533 eyes to determine significance of histologic risk factors by Chantada et al.[22,23]

Low risk (LR):

- Prelaminar optic nerve invasion
- Tumour at lamina cribrosa
- Focal Choroidal Invasion (<3mm)
- Isolated Anterior Chamber Involvement
- Absence of intermediate or high risk features

Intermediate risk (IR):

- Massive choroidal invasion (≥3mm)

- Post laminar optic nerve invasion
- Scleral invasion

High risk (HR):

- Invasion of cut end of optic nerve

Patient with evidence of transscleral invasion or extra-ocular spread on histology will be shifted EO RB protocol

4.2.5 Definition of overall stages

Overall staging will be based on IRSS as detailed below. [8]

1. Stage 0. Patients treated conservatively
2. Stage I. Eye enucleated, completely resected histologically
3. Stage II. Eye enucleated, microscopic residual tumour
4. Stage III. Regional extension
    a. Overt orbital disease
    b. Preauricular or cervical lymph node extension
5. Stage IV Metastatic disease
    a. Hematogenous metastasis (without CNS involvement)
        i. Single lesion
        ii. Multiple lesions
    b. CNS extension (with or without any other site of regional or metastatic disease)
        i. Prechiasmatic lesion
        ii. CNS mass
        iii. Leptomeningeal and CSF disease

4.2.6 Definition of portions of optic nerve on MRI[24]

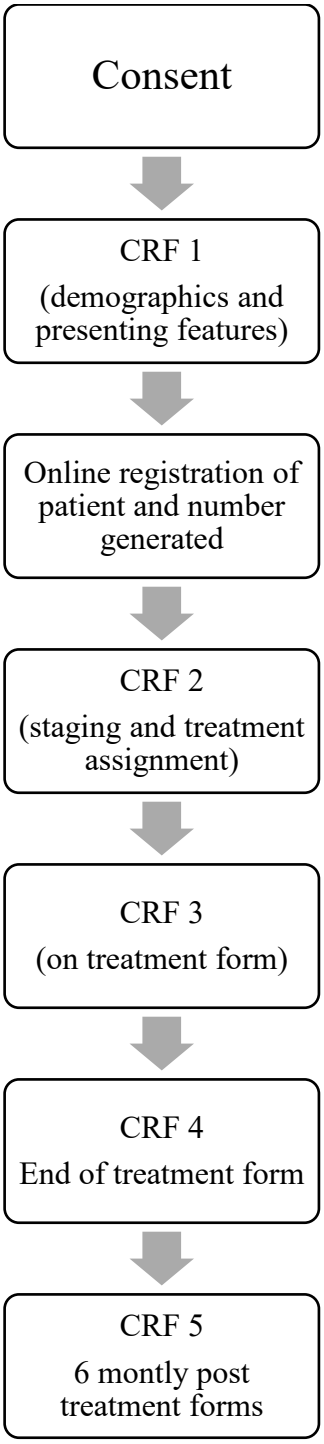
Optic nerve is approximately 50 mm long and is divided into four segments. These are:

1. Intraocular (1 mm) - when it emerges through the scleral opening
2. Intraorbital (25 mm) - the longest segment and communication between subarachnoid space around the optic nerve with that in suprasellar cistern
3. Intracanalicular (9 mm) - as it passes through bony optic canal along with ophthalmic artery (OA)
4. Prechiasmatic (16 mm) - intracranial segment in suprasellar cistern.

5.0 STUDY ENROLLMENT

All patients MUST have a completed and signed Consent Form prior to enrollment on the study.

5.1 Enrollment workflow



CRF 01 (Demographics and presentation): This form must be completed for all patients immediately following diagnosis of RB (unilateral /bilateral and non-metastatic /metastatic RB). Patients for whom a diagnosis of RB is made but either do not survive until initiation of therapy or abandon therapy prior to initiation should also have this form completed.

CRF 02 (Staging and treatment assignment): This form must be completed for all patients who initiated therapy diagnosed with RB (unilateral /bilateral and non-metastatic /metastatic RB) within 2 months of enrollment. Sub-category forms will be used for detailed reporting of individual treatments

CRF 03 (On treatment form): This form must be completed 6 monthly for all patients who initiated therapy for unilateral non-metastatic RB, even those patients who did not complete treatment.

CRF 04 (End of treatment form): This form must be completed for all patients diagnosed with unilateral non-metastatic RB who complete therapy

CRF 05 (Radiation therapy form): This form must be completed only for patients with unilateral non-metastatic RB who received radiation therapy (RT).

CRF 06 (Post treatment follow-up form): This form must be filled for all patients with RB (unilateral /bilateral and non-metastatic /metastatic RB). This form must be completed and submitted at least once every six (6) months as long as the patient remains alive and for a minimum of five (5) years following completion of protocol therapy.

CRF 07 (Relapse/progression reporting form): This form must be completed for all patients who have relapse of their RB after achievement of complete remission (CR) or patients who have progression of disease while on treatment. This must be filled immediately after verification of the relapse. Patients who relapse are considered off protocol but should be followed up, if possible, with reporting on the CR-05 Off Therapy Follow Up form.

CRF 08 (Abandonment reporting form): This form must be completed for all patients who fail to complete planned treatment.

CRF 09 (Death reporting form): This form must be completed for all patients who have confirmation of death (unilateral /bilateral and non-metastatic /metastatic RB). This must be filled immediately after verification of the death. All effort should be made to determine as exact a date of death as possible, for patients who die outside the hospital. Patients who are sent home on terminal care should have a telephone contact made to confirm the date of death.

Note: CRF 03,04,05 will be filled only for patients with unilateral, non-metastatic RB.

6.0 DIAGNOSTIC WORKUP

6.1 Detailed history including past medical history, family history and immunization history.

6.2 Physical examination

6.3 Complete Blood Count

6.4 Serum electrolytes and renal function studies including creatinine and blood urea nitrogen (BUN)

6.5 Hepatic function studies including total and direct bilirubin, alanine aminotransferase (ALT) and albumin.

6.6 Serum calcium, magnesium, phosphate

6.7 Hepatitis serology (Hepatitis BsAg and anti-HCV)

6.8 HIV status testing (serology/PCR)

6.9 PT/PTT

6.10 Chest X-ray

6.11 MRI with contrast orbit and brain protocol under GA/sedation

6.12 Examination under anesthesia (EUA) and B-scan that includes documentation of IIRC stage and following details:

- 6.12.1 Number of tumours
- 6.12.2 Site of tumours
- 6.12.3 Size of tumours
- 6.12.4 Fovea spared or not
- 6.12.5 Intravitrial seeds
- 6.12.6 Subretinal seeds
- 6.12.7 Retinal fluid
- 6.12.8 Retinal detachment

6.13 Cerebrospinal fluid (CSF) examination*

6.14 Bilateral Bone Marrow aspirate and biopsy**.** *

*for patients with IIRC group E and EO RB.

6.15 Measurement of GFR

6.16 Hearing evaluation

7.0 RISK STRATIFICATION

7.1 Stratification

Patients will be categorized into either intra-ocular (IO) or extra-ocular (EO) categories.

For most patients, risk stratification should be completed at time of initial staging based on initial examination and MRI results. If risk classification is changed, based on results of the histopathology testing of patients that undergo upfront enucleation, that should be initiated as soon as that result is available.

7.1.1 Intra-Ocular RB

All of the following features are required to categorize a patient as IO

- No overt extra-ocular disease on examination
- No lymph node involvement
- No extra-ocular disease on MRI
- No extra-ocular disease on histopathology for patients that undergo enucleation.

7.1.2 Extra-Ocular RB

Any one of the following features is enough to categorize a patient as HR

- Overt extra-ocular disease on examination
- Regional lymph node involvement
- Extra-ocular disease on MRI
- Extra-ocular disease on histopathology for patients that undergo enucleation

8.0 CHEMOTHERAPY TREATMENT

8.1 JOE protocol for IO RB

Each course given at approximately 21 day intervals, when the neutrophils are >1x 109/l and platelets >100 x 109/l, total bilirubin and creatinine in normal range.

Audiogram and renal functions (DTPA or creatinine clearance if any rise in creatinine) to be monitored every 3 cycles.

- **Vincristine** day 1 for children > 10Kg

  Dosage: 1.5 mg/m2

  Administration: Intravenous bolus (max total dose 2 mg)

- **Etoposide** day 1

  Dosage: 300mg/m2 for children >10 kg

  Administration: Dilute in 0.9% saline to a maximum concentration of 0.4 mg/ml and infuse over 4 hours.

- **Carboplatin** day 1 for children >10 Kg

  Dosage: 600 mg/m2

  Administration: Dilute to not less than 500 micrograms/ml according to the child's fluid requirements and infuse in 5% dextrose over 1 hour.

  Hydration: The etoposide infusion may act as post-carboplatin hydration ensuring an infusion rate of at least 2.5l/m2/day for a minimum of 4 hours.

8.1.1 Recommendations for children ≤10kg in weight:

- Less than 6 months of age: 50% of calculated dose by body surface area
- 6 months to 1 year of age: 75% of calculated dose by body surface area
- Over 1 year of age: 100% of calculated dose by body surface area

Table 8.1.1.: Chemotherapy for Intra-ocular retinoblastoma

Requirements to begin each cycle: neutrophils >1x 109/l and platelets > 100 x 109/l, total bilirubin and creatinine in normal range.

Audiogram and renal functions (DTPA or creatinine clearance if any rise in creatinine) to be monitored every three cycles

Medication	Dose (per day)	Days	Cycle interval
1. Vincristine	1.5mg/m2	1	21 days
2. Etoposide	300mg/m2	1	21 days
3. Carboplatin	600mg/m2	1	21 days

8.2 CEV for EO RB

Each course given at approximately 21 day intervals, when the neutrophils are >1x 109/l and platelets >100 x 109/l, total bilirubin and creatinine in normal range.

Audiogram and renal functions (DTPA or creatinine clearance if any rise in creatinine) to be monitored every 3 cycles.

- **Vincristine** day 1

  Dosage: 0.025mg/kg

  Administration: Intravenous bolus (max total dose 2 mg)

- **Etoposide** day 1 ,2

  Dosage: 12 mg/kg

  Administration: Dilute in 0.9% saline to a maximum concentration of 0.4 mg/ml and infuse over 4 hours.

- **Carboplatin** day 1

  Dosage: 28mg/kg

  Administration: Dilute to not less than 500 micrograms/ml according to the child's fluid requirements and infuse in 5% dextrose over 1 hour.

  Hydration: The etoposide infusion may act as post-carboplatin hydration ensuring an infusion rate of at least 2.5l/m2/day for a minimum of 4 hours.

Table 8.2.1.: Chemotherapy for extra-ocular retinoblastoma

Requirements to begin each cycle: neutrophils >1x 109/l and platelets > 100 x 109/l, total bilirubin and creatinine in normal range.

Audiogram and renal functions (DTPA or creatinine clearance if any rise in creatinine) to be monitored every 3 cycles

Medication	Dose (per day)	Days	Cycle interval
1. Vincristine	0.025mg/kg	1	21 days
2. Etoposide	12mg/kg	1,2	21 days
3. Carboplatin	28mg/kg	1	21 days

Table 8.2.2: Treatment plan for extra-orbital retinoblastoma			
Cycle number	Date administered	Investigations prior to cycle	Radiation
1		CBC, LFT, Renal Panel, audiogram	
2			
MRI orbit, EUA and surgery if possible*	Surgery date:		
3		CBC, LFT, Renal Panel,	40 Gy in 20 fractions to begin within 4-6 weeks of surgery
4		CBC, LFT, Renal Panel, audiogram, EUA	
5		CBC, LFT, Renal Panel,	
6		CBC, LFT, Renal Panel,	
7		CBC, LFT, Renal Panel,	
MRI orbit and EUA			
8		CBC, LFT, Renal Panel, audiogram, EUA	
9		CBC, LFT, Renal Panel,	
10		CBC, LFT, Renal Panel,	
MRI and EUA and audiogram			
*Surgery may be delayed up to cycle 4 if enucleation is not possible. EUA: exam under anesthesia, CBC: complete blood pictures, LFT: liver function test			

9.0 REQUIRED INVESTIGATIONS:

9.1 At diagnosis

- Please refer section 6.0, Diagnostic workup for required investigations at diagnosis.

9.2 During treatment

- Complete blood count, renal panel, LFT prior to each cycle of chemotherapy
- GFR with DTPA or creatinine clearance if creatinine is elevated
- Hearing assessment after every 3 doses of carboplatin.
- EUA after each cycle of chemotherapy if eye is salvaged.

9.3 At end of treatment

- Complete blood count, renal panel, LFT
- GFR with DTPA or creatinine clearance if creatinine is elevated
- Hearing assessment.
- EUA
- MRI orbit

9.4 Follow up after completion of treatment

9.4.1 Examination of fellow eye

1. 2 to 3 monthly for 6 months,
2. 3 monthly for 12 months,
3. 4 monthly for 12 months,
4. 6 monthly until the age of 10 years.

9.4.2 Renal toxicity monitoring

There is a risk of RTA or glomerular damage by carboplatin. If renal function is normal at end of treatment, then monitor creatinine every 5 years. Get GFR if creatinine is abnormal. Blood pressure monitoring should be done annually.

9.4.3 Ototoxicity monitoring

Perform pure tone audiogram at the end of treatment, as carboplatin carries risk of high tone hearing loss or can be done as child is old enough to co-operate.

Question hearing acuity, speech and language development and school and social functioning annually.

9.4.4 Endocrine monitoring

Patients receiving orbital radiotherapy should be followed up in a joint oncology endocrine clinic in order to monitor for potential anterior pituitary dysfunction.

9.4.5 Secondary tumors:

Carboplatin poses risk of secondary myelodysplasia/myeloid leukemia. Monitor clinically and get CBC if clinical concern.

- Vincristine causes peripheral neuropathy, which resolves with time. Survivors should be monitored by history and exam for persistence of neuropathies

Table 9.0.1: Post Treatment Follow-up Recommendations

Disease monitoring	**Toxicity monitoring**
Clinical examination for relapse/recurrent, metastatic disease. • 2-3 monthly for 6 months • 3 monthly for 12 months • 4 monthly for 12 months • 6 monthly until age 10	End-of-treatment: • Creatinine, Calcium, Electrolytes and Magnesium • GFR (optional) recommended if Creatinine elevated • Pure tone audiogram Repeat 5 yearly Joint oncology/endocrine follow up for patients receiving orbital radiotherapy

10.0 DOSE MODIFICATION FOR TOXICITY

10.1 Carboplatin

10.1.1 For ALT > 5 times the upper limit of normal lasting more than a week reduce vincristine and carboplatin dose by 25% for subsequent doses. Hold start of chemotherapy cycle until ALT under 5 times upper limit of normal.

10.1.2 For two successive cycles delayed > 1 week for low platelets and/or ANC, decrease intravenous carboplatin dose and etoposide dose by 25% for subsequent cycles.

10.1.3 If estimated creatinine clearance using the Schwartz formula drops below the normal range, 24-hour creatinine clearance or radionuclide GFR should be performed.

Carboplatin should be dose-modified as below for renal insufficiency:

Table 10.1.1: Dose-Modification of Carboplatin

GFR	Carboplatin Dose
≥70 mL/min/1.73 m2	600 mg/m2
50- 69 mL/min/1.73 m2	420 mg/m2 (70% of full dose)
25-49 mL/min/1.73 m2	280 mg/m2 (47% of full dose)
< 24 mL/min/1.73 m2	none

11.1.4 For 20 dB loss from baseline hearing at < 2000 Hz, decrease dose carboplatin by 50% for subsequent cycles. For > 20 dB loss at < 2000 Hz delete intravenous carboplatin from subsequent cycles and notify the study chair.

10.2 Etoposide

10.2.1 For two successive cycles delayed > 1 week for low platelets and/or ANC, decrease dose of both carboplatin and etoposide by 25% for subsequent cycles.

10.2.2 Etoposide should be dose-modified as below for renal insufficiency:

Table 10.2.1: Dose-Modification of Etoposide

GFR	Etoposide Dose
> 50 mL/min/1.73 m2	300 mg/m2 (Full dose)
10- 50 mL/min/1.73 m2	225 mg/m2 (75% dose)

< 10 mL/min/1.73 m	150 mg/m2 (50% dose)

10.2.3 Etoposide should be dose-modified as below for hepatic insufficiency [25]

Table 10.2.2: Dose- Modification of Etoposide for Hepatic Insufficiency		
Bilirubin	**AST**	**Etoposide Dose**
26-51 micromol/L	60-180u/L	50% of the dose
> 51 micromol/L	> 180u/L	consider giving 25% of the dose, or omit.

10.3 Vincristine

10.3.1 For severe foot drop, severe paresis, disabling paresthesia or ileus, hold one dose. If toxicity resolves to Grade 1 then resume at 0.025 mg/kg for patients lesser than 10 kg and 0.75 mg/m2 for patients > 10 kg. If symptoms increase to Grade 2 or greater, then discontinue vincristine. If toxicity resolves to less than Grade 1, resume at full dose.

10.3.2 If total bilirubin is > 1.4 x ULN FOR AGE, hold vincristine dose. If total bilirubin is 1.1-1.3 X ULN for age, give 0.025 mg/kg for patients less than 10 kg and 0.75 mg/m2 for patients >10 kg. Check bilirubin prior to next vincristine dose.

For ALT > 5 times the upper limit of normal lasting more than a week reduce vincristine and carboplatin dose by 25% for subsequent doses. Hold starts of chemotherapy cycle until ALT under 5 times upper limit of normal.

11.0 DRUG INFORMATION [26]

11.1 CARBOPLATIN (Paraplatin®)

Source and Pharmacology

The mechanism of action of carboplatin would appear to be similar to that of cisplatin. It binds to replicating DNA causing single strand breaks and interstrand cross-links with DNA. Data suggests that other factors also contribute to cytotoxicity. The α t½ is 1.1 to 2 hours and the β t½ is 2.6 to 5.9 hours. Carboplatin is not protein bound. The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages will require adjustment dependent on the glomerular filtration rate.

Toxicity:

Table 11.1.1: Carboplatin Toxicities

	Common Happens to 21-100 out of every 100 children	**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	Nausea, vomiting	Hypersensitivity reactions[2](anaphylaxis, bronchospasm, hypotension), constipation, diarrhea	Metallic taste, rash, mucositis
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression1 (anemia, neutropenia, leucopenia, thrombocytopenia), electrolyte abnormalities (↓ Na, K, Ca, Mg)	↑ LFTs (alkaline phosphatase, SGOT (AST)), abdominal pain, nephrotoxicity (↓ GFR, ↑ Cr and BUN), asthenia	↑ bilirubin
Delayed: Any time later during therapy		ototoxicity (tinnitus, hearing loss)	Peripheral neuropathy with mild paresthesia, diminished sense of vibration, light touch, pinprick, and joint position, alopecia, temporary loss of vision to light and colors
Late: Any time after completion of treatment			Secondary leukemia
Unknown Frequency and Timing	Fetal toxicities and teratogenic effects of carboplatin have been noted in animals and may cause fetal harm when administered to pregnant women. It is unknown whether the drug is excreted in breast milk		

[1] *Thrombocytopenia is more severe or dose limiting.*

[2] *Hypersensitivity reactions are seen more frequently with repeated courses of therapy (after six courses in adults).*

Formulation and Stability:

Carboplatin is available in 50mg, 150mg, 450 mg and 600 mg vials. It is provided as a premixed aqueous solution or lyophilized powder for injection.

Aqueous Solution

Carboplatin aqueous solution is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin in multidose vials. Unopened vials of carboplatin aqueous solution are stable to the date indicated on the package when stored at 25° C (77° F); excursions permitted from 15°-30° C (59°-86° F). Protect from light. Carboplatin aqueous solution multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25º C following multiple needle entries.

Powder for Injection

Carboplatin powder for injection is a sterile lyophilized white powder in single dose vials containing equal parts by weight of carboplatin and mannitol. Unopened vials of carboplatin are stable to the date indicated on the package when stored at 15°-30° C (59°-86° F). Protect from light.

Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

I.V.

Reconstitute lyophilized powder to concentration of 10 mg/mL with sterile water for injection, 5% Dextrose in Water, or 0.9% Sodium Chloride Injection, USP, or use premixed 10mg/mL aqueous solution. May further dilute in dextrose or sodium chloride containing solutions to a final concentration as low as 0.5 mg/mL. Carboplatin solutions, when prepared as directed are stable for 8 hours at room temperature.

Aluminum can react with carboplatin, causing precipitate formation and potency loss. Do not use needles or IV administration sets containing aluminum parts that may come in contact with carboplatin for the preparation or administration of the drug.

Supplier

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

11.2 ETOPOSIDE IV ONLY

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 G2 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%.

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:

Table 11.2.1: Etoposide Toxicities

	Common Happens to 21-100 out of every 100 children	**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	Nausea, vomiting	Anorexia	Transient hypotension during infusion; anaphylaxis (chills, fever, tachycardia, dyspnea, bronchospasm, hypotension)
Prompt: Within 2-3 weeks, prior to the 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: 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; Sinusoidal obstruction syndrome (SOS formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders including bladder atony, dysuria, polyuria, nocturia and urinary retention; autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss.
Late: Any time after completion of treatment			malignancy (preleukemic or leukemic syndromes)
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

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 controlled room temperature (20˚-25℃ or 68˚-77℉).

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 or 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.

A. Etoposide

Dilute etoposide to a final concentration <0.4 mg/mL in 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP. Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2 mg/mL; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4 mg/mL. Use in-line filter during infusion secondary to precipitate formation risk. However, the use of an in-line filter is not mandatory since etoposide precipitation is unlikely at concentrations of 0.1-0.4 mg/mL.

Do not administer etoposide by rapid intravenous injection. Slow rate of administration if hypotension occurs. Leaching of diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) bags occurred with etoposide 0.4mg/mL in 0.9% sodium chloride solution. To avoid leaching, prepare the etoposide solution as close as possible, preferably within 4 hours, to the time of administration or alternatively as per institutional policy, glass or polyethylene-lined (non-PVC) containers and polyethylene-lined tubing may be used.

B. 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. Use sterile water for injection without benzyl alcohol for neonates and infants < 2 years of age or patients with hypersensitivity to benzyl alcohol.

When reconstituted as directed, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration for 7 days. When reconstituted with a diluent containing a bacteriostat, store at controlled room temperature for upto 48 hours. Following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride Injection store at controlled room temperature for upto 24 hours. Following reconstitution, etoposide phosphate may be further diluted to a concentration as low as 0.1 mg/mL of etoposide with 5% Dextrose Injection or 0.9% Sodium Chloride Injection. The diluted solution can be stored under refrigeration or at controlled room temperature for 24 hours.

Supplier

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

11.3 VINCRISTINE SULFATE (Oncovin®)

Source and Pharmacology:

Vincristine is an alkaloid isolated from Vinca rosea Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes, 2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

Toxicity:

Table 11.3.1: Vincristine Toxicities

	Common Happens to 21-100 out of every 100 children	**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		Jaw pain; headache	Extravasation (rare) but if occurs = local ulceration; shortness of breath and bronchospasm
Prompt: 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: Any time later during therapy			Dystonia, ovarian failure, amenorrhea, anovulatory cycles, hypomenorrhea, onycholysis of nails
Late: Any time after completion of treatment			malignancy (preleukemic or leukemic syndromes)
Unknown Frequency and Timing	Fetal toxicities and teratogenic effects of etoposide have been noted in animals at 1/20th of the human dose. It is unknown whether the drug is excreted in breast milk.		

Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Table 11.3.2: Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Grade	Motor Neuropathy	Sensory Neuropathy
Grade 1	Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.	Paresthesia, pain, or numbness that do not require treatment or interfere with extremity function.
Grade 2	Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.	Paresthesia, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
Grade 3	Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.	Paresthesia or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
Grade 4	Paralysis.	Complete loss of sensation, or pain that is not controlled by narcotics.

Formulation and Stability

Vincristine is supplied in a glass 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℃ or 36-46℉. 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.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of mini-bag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or mini-bag is acceptable.

Injection of vincristine sulfate should be accomplished as per institutional policy. 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.

12.0 SUPPORTIVE CARE GUIDELINES

Routine prophylaxis against pneumocystis carinii pneumonia (PCP) with trimethoprim/sulfamethoxazole (Septran) or other agents should be given.

Routine ophthalmologic topical steroids and other topical medications required for EUA are allowed.

Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes, and general supportive care are to be used as needed per institutional guidelines.

12.1 Blood Product Support

Blood products should be irradiated as per institutional policy.

12.2 Potential drug interactions

There is a potential for drug interaction between fluconazole and vincristine. Fluconazole is now often used for thrush or other minor candida infections in infants. The risk of vinca alkaloid toxicity (e.g., constipation, myalgia, neutropenia) may be increased. This should be avoided if possible and other alternatives used.

12.3 Allergic Reactions

Etoposide

Pre medication with diphenhydramine and steroids and substitution with etoposide phosphate should be considered if a patient develops a reaction that would put him/her at risk if further etoposide were given. Etoposide phosphate would then be given at the same dose and at the same rate as the etoposide.

13.0 ENUCLEATION GUIDELINES

13.1 Indications of Enucleation

a. Retinoblastoma Group D for eyes not salvageable and with no visual potential.
b. Retinoblastoma Group E
c. EO RB after 2-4 cycles of neo-adjuvant chemotherapy

13.2 Surgical Technique

1. Conjunctival Peritomy 360 degrees
2. Isolation and suturing of Extraocular Muscles
3. Clamping the Medial Rectus and Abducting the Eye
4. Retrieving a long stump of the optic nerve at least 15mm
5. Placing an implant and closure in layers

14.0 Radiation Therapy Guidelines

Role of radiation therapy in curative treatment of retinoblastoma has diminished over the last few decades. Although radiation therapy can control local disease due to high radiosensitivity of retinoblastoma, external beam radiation therapy resulted some serious long term effect like asymmetry of face, second malignancy. Therefore, decision to treat children with radiotherapy shall be carefully taken keeping into consideration the other modalities available, long term effects and tumor control.

Radiation therapy for patients on this PSPO protocol for unilateral non-metastatic retinoblastoma shall be decided and planned in close collaboration with dedicated multidisciplinary team comprising of pediatric oncologist, ophthalmologist, radiologist, pathologist and experts from other related specialties. Radiation therapy planning and delivery is to be peer-reviewed with other radiation oncologist having expertise in managing pediatric tumors and have optimal quality assurance systems in place.

It is of utmost importance that all the treatment plans shall be verified by a second clinical medical physicist after the radiation treatment plan made by clinical medical physicist is approved by the treating radiation oncologist. The treatment shall be delivered by a pair of expert and trained radiation therapy technologists to verify correct positioning and treatment delivery.

14.1 General Guidelines

The radiation therapy guidelines for this study are developed specifically for patients with newly diagnosed intraocular and extraocular retinoblastoma. The guidelines are meant to cover specific indications mentioned in section 3.1 and 3.2. This includes patients with positive optic nerve resection margin on histopathology and those who have overt extra-orbital extension of disease or regional lymph node metastases at initial presentation.

14.2 Required Benchmark and Questionnaires

All radiation therapy units (Linear Accelerators) used on this protocol must have their calibrations verified by the national authority – Pakistan Nuclear Regulatory Authority (PNRA). External beam radiation therapy (EBRT) using photons (at least 3-D conformal [3-D CRT] or intensity modulated or volumetric arc therapy [IMRT]) will be allowed in this study. Centers participating in this protocol using 3-D CRT are required to complete the 3-D benchmark; those using IMRT must complete the IMRT quality assurance benchmark and should have attained

relevant quality assurance verification of dose outputs on phantom e.g. head and neck phantom as per benchmark materials and standards of AAPM / ICRU & PNRA.

14.3 Guidelines and Requirements for the Use of IMRT

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

14.4 Indications for Radiation Therapy

Stage II and III patients (orbital and/or regional involvement) will receive radiation therapy (RT) to sites that were initially involved as following

- Stage II: Patient found to have high risk histopathology (positive optic nerve resection margin) after enucleation.
- Stage III: Extra-ocular Disease (Overt extra-orbital disease on exam or MRI, trans-scleral invasion, Lymph node involvement)

14.5 Timing

14.5.1 All patients should be seen in consultation by a radiation oncologist at the time of study enrolment or at least discuss in multi-disciplinary tumor board. The purpose of the consultation is to participate in staging and to review the adequacy of the initial diagnostic imaging studies that will be used for subsequent RT planning.

14.5.2
For Stage II patients, RT shall begin after two cycles of chemotherapy.
For stage III patients, RT shall begin within 4-6 weeks after enucleation.

14.6 Equipment and Methods of Delivery and Verification

Treatment shall be delivered on a Linear Accelerator (LINAC) with photons (4 MV – 10MV) with at least CT based three-dimensional conformal planning. Use of cobalt-60 machines shall be avoided for children being treated with radical intent.

14.6.1 Treatment planning

CT (volumetric) based planning is required to optimize dose to the PTV while protecting normal tissues. Organs within the irradiated volume should be contoured including those required by treatment site. A DVH is necessary to determine target coverage and evaluate dose to normal tissues. In the event that a patient must start emergently with a non-volumetric treatment plan, a volumetric plan will be accomplished as soon as is reasonably possible and the previously utilized beams must be incorporated into the composite plan. CT section thickness should be < 5mm although 2-3mm is preferred.

14.6.2 In-room verification of spatial positioning

14.6.2.1 Portal imaging is the most common system used to verify patient position, in particular when the target volume is believed to possess a fixed spatial relationship with visualized bony anatomy. Orthogonal paired (AP and lateral) portal images (MV or kV) are required for IMRT and 3-D CRT to verify that the isocenter is in correct alignment relative to the patient position.

14.6.2.2 Volumetric imaging is allowed in this study. Cone beam CT (CBCT) can be used for verification as per pediatric protocol. Efforts should be done to avoid unnecessary radiation exposure to normal tissues. This includes in-room kV or MV cone beam or conventional CT imaging. Please record and save representative axial images showing the isocenter and the correct alignment in relationship to the patients' position. For CT tomography where isocenters are not used, a printout of the isodoses overlaid on the fused CT images can be printed to demonstrate in room verification.

14.7 Target Volumes

14.7.1 Standard tumor and target volume definitions

International Commission on Radiation Units and Measurements (ICRU) Reports 50, 62 and 78 (www.icru.org) define prescription methods and nomenclature that will be utilized for this

study. Treatment planning will be based on the following definitions and applies only to the primary tumor site:

• *Gross tumor volume (GTV)* is the volume occupied at diagnosis by visible or palpable disease.

•*Clinical target volume (CTV)* includes the GTV and sites with potential occult tumor involvement including lymph nodes adjacent to the GTV that may be clinically involved.

• *Planning target volume (PTV*) is the CTV surrounded by a geometric margin to account for variability in set-up, breathing or motion during treatment.

14.7.2 Protocol tumor and target volume definitions

14.7.2.1 GTV

GTV is defined as the visible and/or palpable disease defined by physical examination, computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET scan) prior to any surgical debulking or chemotherapy. It also includes enlarged but unresected, regional lymph nodes. For patients who undergo initial surgery, operative notes and pathology reports is usually helpful. For patients with initial tumors that extend into body cavities (i.e., thorax, abdomen) the GTV may require modification. If the tumor has been resected or responded to chemotherapy and the normal tissues have returned to their normal positions, the GTV excludes the volume which extends into the cavity. Examples include tumors which compress but not invade the brain. The GTV must include all infiltrative disease detected at initial presentation.

14.7.2.2 CTV

If there are no sites that warrant irradiation for potential occult tumor, then the CTV is defined as the GTV plus 0.5cm (but not extending outside of the patient).

The CTV will not extend outside of the bony orbit, providing there is no bone erosion of the orbit.

For tumors with no evidence of nodal involvement (N0), the draining regional lymph nodes are not irradiated. When lymph nodes are clinically or pathologically involved with tumor, the entire lymph node drainage chain should be included in the CTV. It would include regional lymph node chains for clinically or pathologically involved nodes including the pre-auricular and ipsilateral neck.

14.7.2.3 PTV

Planning target volume (PTV) is defined as the CTV plus an institutional specified margin to account for day-to-day setup variation related to the ability to immobilize the patient and physiologic motion of the CTV. The minimum margin is 0.5cm but does not have to be uniform in all dimensions. For proton planning, beam specific PTV expansions will be required.

14.8 Target Dose

Integrated boost radiotherapy plans are not permitted.

14.8.1 Dose Definition

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

14.8.2 Prescribed dose and fractionation

The protocol-specified dose per fraction is 180cGy – 200cGy per fraction. The treatment should be limited to one fraction per day. At least two fractions should be given during the first week of treatment. The dose per fractionation may be reduced from 180cGy to 150cGy when large volumes are treated or when tolerance is poor tolerance (i.e., mucositis or diarrhea). The total dose shall be 4000 cGy. Changes to the fractionation regimen should be noted in the treatment record and submitted information.

14.8.3 Dose uniformity

At least 95% of the protocol-specified dose should encompass 100% of the PTV and no more than 10% of PTV should receive greater than 110% of the protocol dose as evaluated by DVH. The 100% isodose should be equal to the prescribed dose. Wedges, compensators and other methods of generating more uniform dose distributions are encouraged.

14.8.4 Tissue heterogeneity

Calculations must take into account tissue heterogeneity and should be performed with CT-based treatment planning to generate dose distributions and treatment calculations from CT densities. When IMRT is used in lung, the heterogeneity correction algorithm must be approved by a verified standard algorithm.

14.8.5 Environment of care - Interruptions, delays and dose modifications

There will be no planned rests or breaks from treatment, and once radiation therapy has been initiated, treatment will not be interrupted except for any life-threatening infection or severe hematologic toxicity defined as ANC < 300/μL or platelets < 40 000/μL during the course of treatment. Under these circumstances, radiation therapy shall be delayed until the counts have recovered. Blood product support should be instituted according to institutional/protocol guidelines. There is no minimum hemoglobin level during radiation therapy. The reason for any interruptions greater than 5 treatment days should be recorded in the patient's treatment chart and submitted with the QA documentation. There should be no modifications in dose fractionation due to age or field size. If any area has been previously treated (emergently), care should be taken not to exceed normal tissue tolerance levels.

14.9 Treatment Technique

14.9.1 Beam Configuration

Every attempt should be made to minimize dose to organs at risk (contralateral optic apparatus and brain etc) without compromising coverage of the target volume. Three-dimensional conformal therapy (coplanar or non-coplanar) or IMRT are required to minimize dose to normal tissues. All efforts would be done to minimize low dose to normal tissues to minimize the risk of second malignancies and other late effects.

14.9.2 Field Shaping

Field shaping for photons will be done with either customized cerrobend blocking or multileaf collimation.

14.9.3 Simulation including patient positioning and immobilization

14.9.3.1 Patient positioning

Reproducible setups are critically important and the use of immobilization devices is strongly encouraged. Consideration should be given to implications for inter and intrafraction motion when using non-standard position approaches.

14.9.3.2 Immobilization devices

Thermoplastic mask and neck rest shall be used to attain reproducible setup which is daily verified.

For IMRT delivery approaches, the methods used for localization and immobilization of both patient and tumor are critical. The imaging studies should provide a clear assessment of the target volume with the patient in the treatment position.

14.9.4 Special considerations

Anesthesia or sedation may be required in certain patients, such as very young patients, to prevent movement during simulation and daily treatments. Expert team for sedation or general anesthesia is required to carry out daily radiation treatment delivery with availability of adequate resources.

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

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

• _A margin of at least 0.5cm should be added to any OAR to form the PRV.

• _For a CTV susceptible to physiologic motion, a margin of at least 0.5cm should be added to the CTV prior to PTV margin expansion or a PTV margin of 1.0cm should be chosen.

14.10 Dose Calculations and Reporting

14.10.1 Prescribed Dose

The dose prescription and fractionation shall be reported on the relevant CRF and the record related to Dosimetry Summary shall be maintained by the treating facility. The total dose delivered shall be reported on the CRF. If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the patient's plan can be directly applied to a phantom geometry.

14.10.2 Normal Tissue Dosimetry

The daily dose to the critical organs indicated should be calculated whenever they are directly included in a radiation field. The total dose shall be calculated and recorded on a standard Total Dose Record form. The appropriate dose-volume histograms should be submitted. If IMRT is used for the primary tumor, a DVH must be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.

15.0 FOCAL THERAPY GUIDELINES

Examination under anesthesia to be scheduled 3 weeks after chemotherapy, and focal therapy applied.

15.1 LASER

Indications

1. Indicated for posteriorly located small (< 3mm) tumors accessible with laser indirect ophthalmoscopy.
2. Large size tumors (>3mm) after chemoreduction.
3. Laser in normal peripheral retina posterior tumor can form a protective barrier to retinal detachment prior to cryotherapy and plaque radiotherapy.
4. It can be used to ablate ischemic retina isolated by extensive scar and protects against neovascularization and vitreous hemorrhage.
5. Recurrent and residual tumors.

Contraindications

1. Tumours with underlying exudative retinal detachment

Method

- *Group A Tumor*: Laser is applied directly on the tumor till a grey white burn covers the entire lesion.
- *Group B and C Tumour*:
    - 1) In a ring like manner around the tumor to coagulate feeding blood vessels leading to ischemic necrosis of tumor.
    - Aggressively on the surface (avoiding hemorrhages) to slowly cook the tumor.
    - In the next 2-3 sessions laser is applied consecutively at 4 weeks' intervals.

Types of lasers

Table 15.1.1: Types of Laser

	Frequency Doubled Nd-YAG	**Semiconductor Diode**
Type of laser	Green	Infrared
Wave length	532nm	810nm
Delivery	Trans-pupillary	Trans-pupillary
Mechanism	Photocoagulation	Photocoagulation/thermotherapy

Penetration	Superficial (~2 mm in non-pigmented tumors) limited by Resultant coagulation and Shorter Wavelength	Deep (4.2 and 5.1 mm, respectively)
Parameters	Power: 0.3 – 0.8 W Duration: 0.5–0.7 s	Power: 0.3 – 1.5 W Duration: 0.5–2.5 s

Laser Approaches

1. Photocoagulation.
2. Thermotherapy.

Complications

1. Vitreous seeding
2. vascular occlusion
3. Preretinal fibrosis
4. Vitreous hemorrhage

15.2 CRYOTHERAPY

- It is used for anterior and small tumors.
- It involves application of below freezing temperature (below- 90.) directly to the tumor mass.
- Triple freeze thaw technique is used through the conjunctiva in two sessions with three weekly intervals.
- Pre-chemotherapy cryotherapy 24–72 hours before chemotherapy maybe used to increase drug penetration into the eye, particularly for vitreous seeding, but not in the presence of retinal detachment
- Cryotherapy through a conjunctival incision may be used for posterior RB refractory to laser focal therapy.

15.3 INTRAVITREAL CHEMOTHERAPY

Indications

1. It can be used when progression or relapse is mostly intravitreal, its retinal source(s) being accessible to focal treatment.

2. Persistent vitreous seeds after systemic intra venous chemotherapy (4cycles) and/or intra-arterial chemotherapy.
3. Recurrent vitreous seeds after completion of treatment.
4. Chemo resistant new vitreous seeds**.**

Contraindications

1. Anterior segment and/or ciliary body invasion.
2. Secondary glaucoma.
3. High bullous retinal detachment.
4. Vitreous hemorrhage obscuring the fundus view.
5. Diffuse vitreous seeding in all four quadrants.

Drugs used

1. Melphalan (25 µg/0.125 ml; 30 µg/0.15 ml).
2. Topotecan hydrochloride (20 µg/0.1 ml with 0.9% normal saline).

Number of Injections

- Six injections are delivered on weekly or biweekly schedule if only one injection is being used.
- Only one or two injections are used if combination of Melphalan and Topotecan is used.

Classification of Intravitreal Seeding

1. Dust

Dust results from a displacement of tumor cells into the vitreous, appears as small granules of vitreous opacities, and can be seen as a vitreous haze overlying tumor.

2. Spheres

Spheres result from translocation of tumor cells into the vitreous, which then undergo clonal expansion into spheres. They are spherically shaped opacities within the vitreous, and dust may be present around them. They can be homogeneously opaque and have a translucent outer shell with a relatively transparent or whitish center.

3. Cloud

Clouds result from massive transference of tumor cells into the vitreous and are typically visualized as a dense collection of punctate vitreous opacities. They can appear as a sheet or globule of seed granules and often with wispy edges, and dust and spheres are sometimes also visible.

Regression Patterns

1. Type 0: not visible.
2. Type I: calcific.
3. Type II: amorphous.
4. Type III: calcific and amorphous configuration.
5. Type IV: Atrophic chorio-retinal flat scar**.**

Surgical Technique and Safety Measures

Although the technique of intravitreal injection appears simple, it carries a risk of extraocular tumor dissemination in tumor-filled eyes. However, modified injection techniques can avoid major complications. Prior to the injection, quadrant and site of injection decided according to the distribution of vitreous seeds. Clinical evaluation of 360° pars plana is essential to detect remote tumor foci for safety. Ultrasound bio microscopy may be used for confirmation. Under aseptic precautions, eye is confirmed, and drug delivered intravitreally via pars plana approach. The needle track size should be kept as small as possible; ideally 32-gauge needle is preferred. Following injection, triple freeze- thaw cryotherapy should be performed at the injection site simultaneously, on withdrawal of the needle. The eyeball is gently jiggled with some forceps for the even distribution of the drug injected and reducing local toxicity. Fundus is examined post-injection for acute complications such as retinal detachment, vitreous and/or retinal hemorrhage. Topical balanced salt solution is used to rinse extraocular chemotherapy from the globe surface to minimize toxicity. Topical steroid/antibiotic is applied, and there is no patch or further eye drops prescribed. Family is instructed to not touch the eye for 1-week.

Complications

Vitreous hemorrhage, cataract, salt-and-pepper retinopathy, and pupil posterior synechia.

16.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY

1. Progressive disease
2. Development of metastatic disease
3. Failure to adhere to protocol therapy. However, if there is variation in timing of enucleation due to logistic or social issues then patient will remain on study and protocol violation will be documented.

17.0 STATISTICAL CONSIDERATIONS

17.1 Sample Size and Sampling Technique

The recruitment of participants will be based on their diagnosis of Retinoblastoma. We will then divide the patients according to laterality and stage of the disease. Patients with unilateral, non-metastatic Retinoblastoma will further be treated with standard of care treatment protocol as described in this study, while patients with bilateral or metastatic Retinoblastoma will be treated as per hospital strategy.

The information for unilateral non-metastatic retinoblastoma will be further divided into intraocular retinoblastoma and extraocular retinoblastoma. The patients with intraocular RB will be further divided into three groups based on the extent of the disease. Group A patients will be treated using focal therapy, Group B/C will receive chemotherapy, and Group D/E will be treated by enucleation followed by chemotherapy regimens.

Pediatric unilateral non-metastatic retinoblastoma is a very rare carcinoma, the recruitment of the participants will be performed using a non-probability purposive sampling technique. The cumulative number of cases expected to report per year from various hospitals around Pakistan is around 200 for unilateral intraocular retinoblastoma and 40 for extraocular retinoblastoma. Assuming that 70% of eligible patients will enroll in this study, the expected number of patients annually becomes 140 for intraocular retinoblastoma and 28 for extraocular retinoblastoma. The original plan for the study is to enroll patients for 2 years, so the total sample size for unilateral intraocular retinoblastoma becomes 280 patients and the total sample size for unilateral extraocular retinoblastoma becomes 56 patients.

As we are collecting information of patients with bilateral and metastatic RB for registry purposes and to look for outcome of these patients. So, sample size calculation is not therefore calculated for such patients.

17.2 Interim Analysis

An interim analysis will be conducted when 50% of patients will be enrolled in each arm.

17.3 Data collection method

Since prospective data collection and submission of data into a central repository is a new function for most of the participating hospitals, it is essential that a close eye is maintained on the quality of the data. Data review and cleaning will be done following enrollment of every increment of 50 subjects. This review will identify missing, incomplete, or illogical data for the essential elements. Any discrepancies, particularly with regards to risk stratification and assignment, will be referred back to the relevant institutional lead for clarification and correction. Delays in timed submission of information will also be relayed back to the leads for their oversight.

Data collection will be done on case report forms (CRFs) specifically designed for this study to collect information on patients' demographics and treatment related factors such as toxicity-related treatment delays. While the hard copies will be maintained in each institution, the data will be submitted to the central PSPO repository through an online, web-based system the front-end for this is built on REDCAP software that replicates the paper based CRFs. The back-end database is built on Microsoft Excel.

17.4 Statistical Analysis

Statistical analysis will be performed using these steps:

1. Descriptive Statistics
2. Univariate and Multivariable Analysis.

17.4.1 Descriptive Statistics

The descriptive statistics of all independent variables and outcome variable will be conducted. Mean and standard deviation of all normally distributed continuous variables will be reported. Median and interquartile ranges (IQR) of all skewed continuous variables will be reported. The frequency and percentages of all categorical variables will be reported. The post hoc power analysis will be performed for accuracy. Mean overall and event free survival will also be estimated for different variables using the Kaplan-Meier method. Log-rank test will be used for testing the overall and event free survival by different independent variables particularly with treatment group.

The Kaplan-Meier curves will be made for looking for assumptions of proportionality of Hazards. If hazards are proportional then Cox proportional algorithm will be used for analysis

otherwise if hazards are not proportional then parametric analysis methods, either Exponential PH or Weibull PH distribution will be used for analysis.

17.4.2 Univariate Analysis

All independent variables will be regressed separately with the outcome variable using appropriate method of survival analysis. The hazard ratio and the confidence intervals will be reported. The significance of all variables will be assessed at a p-values ≤ 0.25. Variables with p-value greater than this or showing results which will not be biologically plausible will be removed and will not be included in the multivariable analysis.

17.4.3 Multicollinearity

All variables with p-value ≤ 0.25 were assessed for multicollinearity between variables. Pearson's Correlation Coefficient will assess multicollinearity of two continuous quantitative variables, multicollinearity between two categorical variables will be assessed by Cramer's V test and multicollinearity between categorical and continuous quantitative variables will be assessed by ETA test. A correlation of greater than 0.8 indicates multicollinearity. In case if multicollinearity is present, we will drop the variable with a lower hazard ratio.

17.4.4 Multivariable Analysis

A stepwise model building approach will be employed to construct a multivariable model. All the variables which will be significant in the univariate analysis and will have no multicollinearity will be added to the model at a significance level <0.05. Later, we will assess for biologically plausible interaction and confounding in the model.

18.0 ETHICAL CONSIDERATIONS

This is essentially a single arm study, utilizing treatment strategies that are considered standards. The primary objective of this study is to collect data regarding total number of patients with retinoblastoma, their disease characteristics, and outcomes, and to standardize care for unilateral non-metastatic retinoblastoma across Pakistan. While the treatment proposed in this protocol is not directly and completely derived from an existing reported clinical trial, the modifications made are based on well-established treatment strategies that have been included due to local, patient-specific or Infrastructure-specific circumstances.

Each individual institution will be required to partner with the Pakistan Society of Pediatric Oncology (PSPO) as a collaborating institution. An institutional lead will be identified, who will be responsible for the administration of the protocol therapy and the collection of the required data.

Ethical review will be required from each individual institution, prior to initiation of the study.

All patients will undergo an informed consent process before enrollment, this signed consent will be made part of the required documentation.

Identifying information will be collected, as this will be required for data verification and to prevent duplication in case patients move from one hospital to another. This information will be kept confidential and any presentation of the data derived from this study will be completely anonymized. Patients and their families will have the right to refuse participation in the study, and to withdraw from the study at any Time-point; this will not impact their ability to receive care at that or any other Hospital.

Data derived from any specific institution will remain the property of that particular Institution. Inclusion of the data in any analysis, presentation or publication will be done only following permission of the Institutional Lead. Institutions will have the right to withdraw from the study at any time. Any presentation or publication will be done by a Writing Committee that will be led by the Study Principal Investigators or their Designees.

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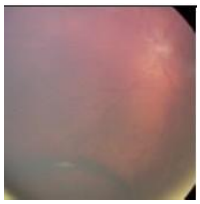
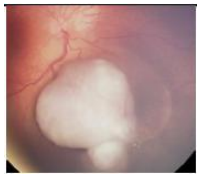
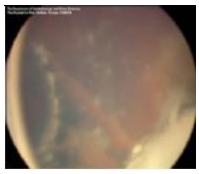
Appendix I: International Intraocular Retinoblastoma Classification

Table 12: International Intraocular Retinoblastoma Classification (IIRC)	
Group A: Very low risk	
Small discrete tumours not threatening vision(T1a)	
All tumours are 3mm or smaller confined to theretina	
Located atleast 3mm from the foveola and 1.5mmfrom the optic nerve	
No vitreous or subretinal seeding	
Group B: Low risk	
No vitreous or subretinal seeding (T1b)	
Tumours any size or location not in group A	
No vitreous or subretinal seeding	
Subretinal fluid no more than 5mm from tumourbase	
Group C: Moderate risk (T2)	
Focal vitreous or subretinal seeding and discrete retinal tumours of any size and location	
Local, fine and limited seeding (T3)	
Discrete intraretinal tumours of any size andlocation (T2b)	
Up to one quadrant of subretinal fluid (T2a)	
Group D: High risk	
Diffuse vitreous or subretinal seeding (T3b)	
Diffuse intraocular disseminated disease	
Extensive or “greasy” vitreous seeding	
Subretinal seeding may be plaque like	
More than one quadrant retinal detachment	
Group E: Very high risk (T4a)	
Very high risk with one or more of the following:	
Irreversible neovascular glaucoma	
Massive intraocular hemorrhage	
Aseptic orbital cellulitis	

Tumour anterior to anterior vitreous base	
Tumour touching the lens	
Diffuse infiltrating RB	
Phthisis or pre-phthisis	

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Appendix II: Histopathology Reference for Reporting

College of American Pathologist Protocol for the Examination of Specimens from Patients with Retinoblastoma should be used as standard for reporting of enucleation specimen.

It can be accessed at this link

Retinoblastoma_4.1.0.0.REL_CAPCP.pdf
https://documents.cap.org/protocols/Retinoblastoma_4.1.0.0.REL_CAPCP.pdf

Appendix III: MRI Protocol in Retinoblastoma

REQUIREMENTS:

1. Scanner and coils:

   - Field strength above 1T
   - 1.5-T system combined with one or two small surface coils (diameter < 5 cm)
   - 3.0-T system combined with multichannel head coil

2. MRI Sequences (Minimum Requirements):

   a) Orbits:

      - Transaxial T2-W (slice thickness ≤ 2 mm)
      - Optional: Transaxial CISS (Siemens) / FIESTA (GE) / DRIVE (Philips)

   b) Eye(s) and Optic Nerve(s):

      - In-plane pixel size < 0.5 × 0.5 mm; slice thickness ≤ 2 mm
      - Unilateral disease (or bilateral disease with only one eye strongly affected)
      - Precontrast T1-W; at least one plane: transaxial or sagittal oblique
      - T2-W; at least one plane: transaxial or sagittal oblique
      - Postcontrast T1-W, no FS; transaxial and sagittal oblique
      - Bilateral disease (both eyes strongly affected)
      - Precontrast T1-W (transaxial)
      - T2-W (transaxial)
      - Postcontrast T1-W, no FS; sagittal oblique of both eyes and transaxial

   c) Brain:

      - Transaxial T2-W (slice thickness ≤ 4 mm)
      - Postcontrast T1-W (2D SE with slice thickness ≤ 3 mm or 3D GRE ≤ 1 mm

(FS fat-saturation, *SE* spin-echo, *GRE* gradient-echo)

Consensus among members of the European Retinoblastoma Imaging Collaboration (ERIC)

MRI FINDINGS IN EXTRAOCULAR RETINOBLASTOMA

- Invasion of sclera.
- Invasion with enhancement into retrobulbar fat.
- Size of optic nerve above normal.
- Abnormal signal in optic nerve on T2WI
- Optic nerve enhancement of more than 3mm. (Post laminar optic nerve invasion)
- Extension / abnormal signals of meningeal sheath along optic nerve.
- Presence of preauricular lymph nodes.

References:

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256324/
2. https://ejrnm.springeropen.com/articles/10.1186/s43055-020-0143-3
3. http://www.ajnr.org/content/early/2021/01/28/ajnr.A6949

Appendix IV: Consent Form

Informed Consent

Project Information	
Project Title: **National Standard of Care Protocol for Treatment and Management of Retinoblastoma (PSPO-RB-22-01)**	Version & Date:
ERC Project No:	Sponsor: Pakistan Society of Pediatric Oncology (PSPO)
Principal Investigator: Dr. Haleema Saeed	Organization: Shaukat Khanum Memorial Cancer Center
Location:	Phone:
Other Investigators:	Organization:

I am Dr. Haleema Saeed (or name of institutional PI) from the Department of Oncology; Shaukat Khanum Memorial Cancer Center (or the name of the relevant participating institution) and we are doing a research protocol to improve treatment for children with Retinoblastoma (RB) across Pakistan.

Retinoblastoma (RB) is the most frequent kind of cancer of the eye in children. Treatment for RB involves different types of treatment, including a combination of focal therapy (for example laser or cryotherapy), chemotherapy, surgery, and radiation. The aim is to conduct a National Standard of care study for the treatment and management of all patients diagnosed with Retinoblastoma at all institutions across Pakistan. We are interested in studying the presentation and outcome of RB patients and want to access the effects of national standardized treatment for unilateral non-metastatic Retinoblastoma, resulting in greater accuracy in diagnosis and improved survival.

PURPOSE OF THIS RESEARCH STUDY

You are being asked to participate in a research study designed to collect and analyze information on how children who have been diagnosed with RB (irrespective of its laterality and stage) present and respond to treatment.

We will also study the effect of treatment of patients with unilateral non-metastatic RB according to a standardized protocol.

We believe that the management and treatment according to a standard treatment protocol for children with unilateral non-metastatic retinoblastoma will allow greater accuracy in diagnosis and improved survival.

DESCRIPTION OF THE RESEARCH STUDY

You are being asked to participate in the study because your child has been diagnosed with RB. Patients with RB get classified into two different groups based on certain clinical, laboratory, and radiology results and are treated accordingly.

In this protocol, we will be collecting information about your child's presentation and stage of disease. If your child has disease in both eyes or metastatic disease then treatment will be according to the individual hospital guidelines.

If your child has disease in only one eye and is not metastatic, we will be categorizing your child's unilateral non-metastatic RB into two groups Intraocular Retinoblastoma and Extraocular Retinoblastoma. Intraocular means that the tumor remains inside the eye, while extraocular means that the tumor has spread outside the eye. Further staging will be based according to the guidelines of the International Retinoblastoma Staging System (IRSS).

All patients will be treated according to a treatment protocol that is based on international standards and our local conditions.

We will be collecting data regarding your child's clinical and laboratory results, the treatment your child receives, and how they respond to the treatment.

POSSIBLE RISKS OR DISCOMFORT

There are no additional risks in participating in this study.

POSSIBLE BENEFITS

This study is not designed to benefit you directly. The study results will be used to better understand this disease in children in Pakistan.

FINANCIAL CONSIDERATIONS

You will not receive any financial compensation or benefits from this study.

AVAILABLE TREATMENT ALTERNATIVES

You can decide whether you want to be in this study or not. Patients not interested in the study will be offered treatment with the same or similar standard treatment. However, the data regarding the patient's disease and the outcome will not be collected and used.

AVAILABLE MEDICAL TREATMENT FOR ADVERSE EXPERIENCES

The risk of side effects are those associated with the treatment of the RB. These side effects will be discussed in detail by your doctor when they discuss the details of the therapy. There is no additional risk of adverse events that are due to participation in this study.

CONFIDENTIALITY

Your privacy will be maintained by removing any identifying information. There will be limited access to the details; access will be available to the research team only. However, any records or data obtained as a result of your participation in this study may be inspected by the hospital's Ethics Research Committee members.

Once data collection is complete, all participant information, which is helpful to identify the patient will remain confidential. This will only be disclosed with your permission or as required by law. Confidentiality will be maintained by providing unique Id numbers to each participant and the data will be kept in password protected files. To ensure privacy, all information that could identify the patient (e.g., name, medical record number, etc.) will be removed from the data. Your child's identity will be kept private during this study. The study's findings, including any laboratory or other data, may be published for scientific purposes, but your name or any identifiable references to you will not be included.

RIGHT TO REFUSE OR WITHDRAW

You are free to choose whether or not to participate in this study. There will be no penalty or loss of benefits to which you are otherwise entitled if you choose not to participate.

You will be provided with any significant new findings developed during the course of this study that may relate to or influence your willingness to continue participation. In the event you decide to discontinue your participation in the study, please notify Dr. Haleema Saeed (telephone no:_____) or her designate of your decision so that your participation can be orderly terminated.

In addition, your participation in the study may be terminated by the investigator without your consent under certain circumstances that include the inability to move forward with the study or in the event that they believe it is in your child's best interest or if you were to object to following the treatment plan or any future changes that may be made in the study plan.

For your safety, however, you should consider the doctor's advice about how to go off the study treatment. If you leave the study before the final planned study visit, the researchers may ask you to have some of the final steps done.

AVAILABLE SOURCES OF INFORMATION

Any further questions you have about this study will be answered by the Principal Investigator:

Name: Dr. Haleema Saeed

Phone Number: +92 42 5905000 (Ext 4032)

Any questions you may have about your rights as a research subject will be answered.

Name: Institutional PI Name

Phone Number: Institutional PI Number

In case of a research-related emergency, call:

Day Emergency:

Name:

Number:

AUTHORIZATION

I have read and understood this consent form, and I volunteer to participate in this research study. I understand that I will receive a copy of this form. I voluntarily choose to participate, but I understand that my consent does not take away any legal rights in the case of negligence or other legal faults of anyone who is involved in this study.

Name of patient / participant (Printed or Typed): _____

_____

Name of parent/legal guardian: _____

Signature of patient / participant (*optional)*: _____

_____

Signature of parent/legal guardian: _____

Relationship: _____ Date: ____/____/_____Time: _____

Signature of Principal Investigator: _____

Date: ____/____/_____ Time: _____

Name and Signature of Person obtaining consent: _____

Date: ____/____/_____ Time: _____

Appendix V: Assent Form

ASSENT TO PARTICIPATE IN THE RESEARCH

Project Information	
Project Title: **National Standard of Care Protocol for Treatment and Management of Retinoblastoma**	Project Number:
ERC Project No:	Sponsor: Pakistan Society of Pediatric Oncology (PSPO)
Principal Investigator: Dr. Haleema Saeed	Organization:
Location:	Phone:
Other Investigators:	Organization:

You are being asked to participate in a research study conducted by Dr. Haleema Saeed (or name of institutional PI) from the Department of Oncology at Shaukat Khanum Memorial Cancer Center (or name of institutional PI). You were selected as a possible participant in this study because of your diagnosis of Retinoblastoma. Your participation in this research study will be completely voluntary.

Why are we doing this study?

The aim is to conduct a National Standard of care study for the treatment and management of all patients diagnosed with Retinoblastoma at multiple institutions across Pakistan. We are interested in studying the presentation and outcome of RB patients and want to assess the effects of national standardized treatment for unilateral non-metastatic Retinoblastoma, resulting in greater accuracy in diagnosis and improved survival.

What will happen if I take part in this research study?

Please talk this over with your parents before you decide whether or not to participate. We will also ask your parents to give their permission for you to take part in this study. Even if your parents say "yes" you can still decide not to participate.

If you volunteer to be in this study, you may leave the study at any time without consequences of any kind. You are not waiving any of your legal rights if you choose to be in this research study. You may refuse to answer any questions that you do not want to answer and remain in the study.

How long will I be in the research study?

You will be recruited in the study for approximately two years, depending on your diagnosis. Later we will follow each patient for five years. All your records will be collected from your patient files.

Are there any potential risks or discomforts that I can expect from this study?

There are no potential risks and discomforts in this study.

Are there any potential benefits if I participate?

The study has not been designed to benefit you directly. The study results will later be used to better understand and maintain a standard treatment approach for all patients with the disease in Pakistan.

Will I receive any payment if I participate in the study?

You will not receive any financial compensation or payment for participation from this study.

Will information about me and my participation be kept confidential?

All participant information, which is helpful to identify the patient will remain confidential. This will only be disclosed with your permission or as required by law. Confidentiality will be maintained by providing unique Id numbers to each participant and the data will be kept in password protected files. To ensure privacy, all information that could identify the patient (e.g., name, medical record number, etc.) will be removed from the data once it has been collected. Your identity will be kept private during this study. The study's findings, including any laboratory or other data, may be published for scientific purposes, but your name or any identifiable references to you will not be included.

Who can answer questions I might have about this study?

If you have any questions, comments, or concerns about this study, you can talk to one of the researchers. Please contact Any further questions you have about this study will be answered by the Principal Investigator:

Name: Dr. Haleema Saeed
Phone Number: +92 42 5905000 (Ext 4032)
Any questions you may have about your rights as a research subject will be answered.

Name: Dr. Haleema Saeed
Phone Number: +92 42 5905000 (Ext 4032)
In case of a research-related emergency, call:
Day Emergency:
Name:
Number:

This study has been reviewed and approved by _____ Ethics Review Committee.

Signature Section for Assent:

I, _____ (your name) would like to be in this research study. I understand the procedures described above. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

If the child not able to read/write, verbal assent received: Yes ☐ No ☐ Not Applicable ☐

Name of the Participant: _____

Signature of the Participant: _____ Date: _____

Name of the Witness: _____

Signature of the Witness: _____ Date: _____

Name and Signature of Person Obtaining Consent: _____

Date: _____

Appendix VI: Case Report Forms (CRFs)

RB-CRF 01 Registration Form:

This form must be completed for all patients immediately following the diagnosis of RB (unilateral /bilateral and non-metastatic /metastatic RB). Patients for whom a diagnosis of RB is made but either do not survive until initiation of therapy or abandon therapy prior to initiation should also have this form completed.

1. Which hospital is this patient being treated in? _____
2. What is the patient's full name? _____
3. What is the name of the patient's Father? _____
    a. Father's NIC number: __ __ __ __ __ - __ __ __ __ __ __ __ - __
4. What is the name of the patient's Mother? _____
    a. Mother's NIC number: __ __ __ __ __ - __ __ __ __ __ __ __ - __
5. If NIC number not available for either parent, then NIC number of accompanying, responsible individual: __ __ __ __ __ - __ __ __ __ __ __ __ - __
    a. Relationship: _____
6. What is the patient's date of birth? ___/___/_____ (dd/mm/yyyy)
    a. *Please provide a date of birth and not age here. For patients whose dates of birth cannot be determined exactly, please question the parents critically and make a closest estimate of the birth date.*
7. Sex: ___ Male ___Female
8. Date of presentation to oncologist: ___/___/_____ (dd/mm/yyyy)
    a. *This should be the date the patient was first seen in your institution for this condition; this could be in the outpatient setting or admitted to the inpatient ward.*
9. Duration of symptoms in months: _____
10. Presenting symptom (choose all the apply)
    a. White reflex

b. Strabismus

c. Eye redness

d. Eye swelling

e. Loss of vision

f. Other _____

11. Family history of ocular malignancy: __yes ___no

a. If yes, which family member is effected

12. Education level of father: _____

13. Education level of mother: _____

14. Area of or origin/residence: _____

a. City/village: _____

b. Province: _____

c. Country: _____

15. Did the patient start RB-directed therapy? YES ___ NO ___

15.1 If NO, please provide reason:

15.1.1 Death ___;

15.1.2 Date of death ___/___/_____ (dd/mm/yyyy)

15.1.2.1 Cause of death; _____

15.1.2.2 Disease progression

Infection ___

Other, specify:

_____

15.1.3 Treatment Abandonment _____

RB-CRF 02 Staging and Treatment Assignment Form

This form must be completed for all patients who initiated therapy diagnosed with RB (unilateral /bilateral and non-metastatic /metastatic RB) within 2 months of enrollment. Sub-category forms will be used for detailed reporting of individual treatments.

1. **EUA findings (fundus drawing to be uploaded)**

   Laterality: Right _____ Left _____ Bilateral _____

Right Eye:

Not applicable_____ (*choose this if patients has unilateral disease and Right eye is not involved)*

a. Number of lesions: ____
b. Size of lesion: 1. _____ 2. ____ 3. _____
c. Location of lesion: 1. _____ 2. _____ 3._____
d. Fovea spared: Yes _____No _____
e. Intravitreal seeds: Yes _____No _____
f. Subretinal seeds: Yes _____No _____
g. Retinal fluid: Yes _____No _____
h. Retinal detachment: Yes _____No _____
i. Intra-ocular pressure _____

Left Eye:

Not applicable_____ (*choose this if patients has unilateral disease and Left eye is not involved)*

j. Number of lesions: ____
k. Size of lesion: 1. _____ 2. ____ 3. _____
l. Location of lesion: 1. _____ 2. _____ 3._____
m. Fovea spared: Yes _____No _____
n. Intravitreal seeds: Yes _____No _____
o. Subretinal seeds: Yes _____No _____
p. Retinal fluid: Yes _____No _____
q. Retinal detachment: Yes _____No _____
r. Intra-ocular pressure _____

2. **Group (IIRC):**

Right eye: A ___B ___C ___D___ E___ Not applicable _____

Left eye: A ___B ___C ___D___ E___ Not applicable _____

3. MRI finding

Laterality: Right _____ Left _____ Bilateral

Right Eye:

Not applicable_____ (*choose this if patients has unilateral disease and Right eye is not involved)*

a. Number for lesions: _____
b. Size of lesion: 1. _____ 2. _____ 3. _____
c. Optic nerve enhancement: Yes _____No _____
d. Optic nerve thickening: Yes _____No _____
e. Extent of optic nerve involvement:
    i. Intraocular
    ii. Intraorbital
    iii. Intracanalicular
    iv. Prechiasmatic
f. Extra-ocular extension: Yes _____No _____

- If yes, then choose all that apply:
    - Invasion of sclera.
    - Invasion with enhancement into retrobulbar fat.
- Optic nerve enhancement of more than 3mm. (Post laminar optic nerve invasion)
- Extension / abnormal signals of meningeal sheath along optic nerve.
- Presence of preauricular lymph nodes.

Left Eye:

Not applicable_____ (*choose this if patients has unilateral disease and Right eye is not involved)*

g. Number for lesions: _____
h. Size of lesion: 1. _____ 2. _____ 3. _____
i. Optic nerve enhancement: Yes _____No _____
j. Optic nerve thickening: Yes _____No _____
k. Extent of optic nerve involvement:
    i. Intraocular
    ii. Intraorbital
    iii. Intracanalicular
    iv. Prechiasmatic
l. Extra-ocular extension: Yes _____No _____

- If yes, then choose all that apply:
    - Invasion of sclera.
    - Invasion with enhancement into retrobulbar fat.
- Optic nerve enhancement of more than 3mm. (Post laminar optic nerve invasion)
- Extension / abnormal signals of meningeal sheath along optic nerve.
- Presence of preauricular lymph nodes.

m. Intracranial extension: Yes _____No _____

4. Histologic findings in case of upfront enucleation

i. Number of tumor foci _____
ii. The degree of the optic nerve invasion
    1. Prelaminar _____
    2. Laminar _____
    3. Retrolaminar _____
iii. Tumor at optic nerve surgical margins
    1. Yes _____No _____
iv. Focal Choroidal Invasion (< 3mm invasion)
    1. Yes _____No _____
v. Massive Choroidal Invasion (≥3mm invasion)
    1. Yes _____No _____
vi. Intrascleral infiltration
    1. Yes _____No _____
vii. Transscleral Invasion
    1. Yes _____No _____
viii. Extraocular spread. Yes _____No _____

5. Overall stage (IRSS) (*please select based on worse eye in case of bilateral disease***)**

0 (treated conservatively)

I (intra-ocular)

II (microscopic residuum)

III (overt orbital/Lymph node)

IV (metastatic)

6. Side of Metastasis:

a. None
b. CSF

c. Bone marrow
d. Brain
e. Bone
    i. *Patients with metastatic disease will be excluded from treatment portion of study*

7. Treatment group assignment

i. IO RB _____
ii. EO RB ____
iii. Institutional guidelines/national guidelines in case of bilateral and metastatic disease

8. **Histologic Risk group assignment in case of upfront enucleation:**

i. Low risk
ii. Intermediate risk
iii. High risk
iv. Extra-ocular

RB-CRF 03 On Therapy Form

This form must be completed 6 monthly for all patients who initiated therapy for unilateral non-metastatic RB, even those patients who did not complete treatment.

Note: CRF 03, 04 and 05 will be filled only for patients with unilateral, non-metastatic RB.

1. Patient followed up date ___/___/_____ (dd/mm/yyyy)
2. Type of follow up? *Check only one that is applicable*
    i. Clinic visit _____
    ii. Telephone contact with family_____
    iii. Information received through other sources_____
        1. Please specify: _____
3. Vital status at follow-up
    i. Alive _____
    ii. Dead _____ (*if dead fill the death form and CRF 4)*
4. Disease status at follow up
    a. Ongoing treatment
    b. Treatment abandonment (fill abandonment form and CRF 4)

RB-CRF 04 End of Treatment Reporting Form

This form must be completed for all patients diagnosed with unilateral non-metastatic RB who complete therapy

Note: CRF 03, 04 and 05 will be filled only for patients with unilateral, non-metastatic RB.

1. End of treatment date (dd/mm/yyyy):
2. Status at EOT: ___eye enucleated (no residual disease) _____ eye salvaged (lesion fully calcified _____ eye salvaged (partially calcified) _____ did not complete treatment due to abandonment, progression or death (fill relevant form)
3. Was enucleated recommended to the patient?
    i. Yes _____ No _____
4. Did the patient undergo enucleation at the recommended time?
    i. Yes _____ No _____
5. Date of Enucleation of the Tumor? date ___/___/_____ (dd/mm/yyyy)
    1. If Yes, what was the time of surgery?
        a. Upfront _____
        b. During Chemotherapy _____
        c. After Chemotherapy _____
        d. At Relapse _____
6. What were the microscopic findings on Histopathology reports if not already reported in initial staging form-CRF02 (*this will be in all cases except those with upfront enucleation*)?
    i. Percentage of viable tumour: _____
    ii. Number of tumor foci _____
    iii. The degree of the optic nerve invasion
        1. Prelaminar _____
        2. Laminar _____
        3. Retrolaminar _____
    iv. Tumor at optic nerve surgical margins
        1. Yes _____ No _____
    v. Focal Choroidal Invasion (< 3mm invasion)
        1. Yes _____ No _____
    vi. Massive Choroidal Invasion (≥3mm invasion)

1. Yes _____ No _____

vii. Intrascleral infiltration

1. Yes _____ No _____

viii. Transscleral Invasion

1. Yes _____ No _____

7. Was intra-venous chemotherapy given to patient?
   i. Yes _____ No _____
      1. If Yes, what was the number of sessions? _____
      2. What protocol was used?
         a. IO RB-Carboplatin/ Etoposide/ Vincristine (JOE) _____
         b. EO RB- Carboplatin/ Etoposide/ Vincristine (CEV) _____
8. Was Cryotherapy given to the patient?
   i. Yes _____ No _____
      1. If Yes, what was the number of sessions? _____
9. Was laser therapy provided to patient?
   i. Yes _____ No _____
   ii. If Yes, what was the number of sessions? _____
      1. If yes, what was the type of laser used?

         Green laser_____

         Diode laser_____
10. Was intra-vitreal chemotherapy given to patient?
    i. Yes _____ No _____
       1. If Yes, what was the number of sessions? _____
       2. If yes, what agent was used? _____
11. Was intra-arterial chemotherapy given to patient?
    i. Yes _____ No _____
       1. If Yes, what was the number of sessions? _____
       2. What agent was used?
          a. Melphalan _____
          b. Topotecan _____
       3. What was the indication for use?
          a. Primary treatment _____

b. Refractory disease _____

12. Is further focal therapy planned?

i. Yes _____ No_____

If yes, then questions question 8-11 to be filled again in 6 months

13. Was radiation given to patient?

i. Yes _____ No _____ (*if yes fill radiation form)*

RB-CRF 05 Radiation Therapy Form

This form must be completed only for patients with unilateral non-metastatic RB who received radiation therapy (RT).

Note: CRF 03, 04 and 05 will be filled only for patients with unilateral, non-metastatic RB.

1. In which institution was the Radiation Therapy administered?

    a. ____ AEMC-AECH at JPMC (Atomic Energy Medical Center), Karachi
    b. ____KIRAN-AECH (Karachi Institute of Radiotherapy & Nuclear Medicine), Karachi.
    c. ____ZMU (Ziauddin Medical University), Karachi.
    d. ____AKUH (Aga Khan University Hospital), Karachi.
    e. ____ INMOL-AECH (Institute of Nuclear Medicine & Oncology), Lahore
    f. ____ SKMCH&RC (Shaukat Khanum Memorial Cancer Hospital & Research Center) Lahore.
    g. ____ NORI-AECH (Nuclear Medicine Oncology & Radiotherapy Institute), Islamabad.
    h. ____ CMH-RWP (Combined Military Hospital), Rawalpindi.
    i. ____ SIH (Shifa International Hospital), Islamabad.
    j. ____ IRNUM-AECH, Peshawar.
    k. ____ SKMCH&RC (Shaukat Khanum Memorial Cancer Hospital & Research Center) Peshawar.
    l. ____ CENAR-AECH (Centre for Nuclear Medicine and Radiotherapy), Quetta.
    m. ____ MINAR-AECH, Multan.
    n. ____ NMC (Nishtar Medical Center & Hospital), Multan.

2. What was the **total dose** given of radiation therapy given to this patient?

    a. Total Dose: _____
    b. No. of fractions: _____

3. In how many phases the treatment was delivered?

    _____ Single Phase _____ Two Phases _____ Other

4. What was the dose delivered in Phase I?

    a. Total Dose: _____
    b. No. of fractions: _____
    c. Dose per fraction: ____

5. What was the dose delivered in Phase II?

    a. Total Dose: _____
    b. No. of fractions: _____

c. Dose per fraction: ____

6. What was the volume treated in Phase I?
    i. Orbit Only
        1. _____ Right
        2. _____ Left
    ii. Neck Region
        1. _____ Right
        2. _____ Left
    iii. Preauricular Region
        1. _____ Right
        2. _____ Left
    iv. Orbit + Optic Canal
        1. _____ Right
        2. _____ Left
    v. Orbit, optic canal and partial brain
        1. _____ Right
        2. _____ Left
    vi. Other
        1. _____

7. What machine has been used for Radiotherapy?
    1. Cobalt-60 _____
    2. Linac _____
    3. Other _____
8. What is the planning system of radiation therapy used for treatment planning and delivery?

    _____
9. What are the particles used?
    a. Photons:

        Energy _____
    b. Electrons

        Energy _____
10. What was the technique of Radiation therapy?
    i. _____ 2D
    ii. _____ 3DCT

iii. _____ IMRT

iv. _____ VMAT

v. _____ Other

11. Were the details of this patient discussed in tumor board meeting?

____Yes ____No

12. Was the radiation treatment plan discussed or peer reviewed with other radiation oncologists?

____Yes ____No

13. When was the CRT administered?

a. Start date ___/___/_____ (dd/mm/yyyy)

b. End date ___/___/_____ (dd/mm/yyyy)

RB-CRF 06 Off Therapy Follow-up Form

This form must be filled for all patients with RB (unilateral /bilateral and non-metastatic /metastatic RB). This form must be completed and submitted at least once every six (6) months as long as the patient remains alive and for a minimum of five (5) years following completion of protocol therapy.

1. Completion of therapy date ___/___/_____ (dd/mm/yyyy)

Date of completion of therapy needs to be recorded only once. On subsequent follow up visits only the information below needs to be filled.

2. Patient followed up date ___/___/_____ (dd/mm/yyyy)

3. Type of follow up? *Check only one that is applicable*

    i. Clinic visit _____
    ii. Telephone contact with family_____
    iii. Information received through other sources_____
        1. Please specify: _____

4. What is the Disease status at follow-up? *Check only one that is applicable*

    i. Remission CR1 _____
    ii. Remission CR 2 _____
    iii. Relapse on second line treatment (fill relapse form) _____
    iv. Relapse on palliation (fill relapse form) _____
    v. Progressive disease _____
    vi. Secondary malignancy (SMN) _____
        1. Specify _____

5. Vital status at follow up

    i. Alive _____
    ii. Dead _____ (*if dead fill the death form)*

6. Long term complications of therapy at follow-up

    i. Renal impairment: Yes _____ No _____ Not Checked _____
        1. If Yes, Please specify _____
    ii. hearing impairment: Yes _____ No _____ Not Checked _____
        1. If Yes, Please specify _____
    iii. endocrine complications Yes _____ No _____ Not Checked _____

1. If Yes, Please specify _____

7. Pure tone audiogram: Normal ___ Abnormal ____ Not done ___
8. Endocrine follow up (for patients receiving orbital radiotherapy)

   Clinical impression of hypothalamic-pituitary axis involvement Yes _____ No _____

   Hormonal assay (if advised)

   HP dysfunction: Yes _____ No _____

   Therapy offered: Yes _____ No _____

RB-CRF 07 Relapse Reporting Form

This form must be completed for all patients who have relapse of their RB after achievement of complete remission (CR) or patients who have progression of disease while on treatment. This must be filled immediately after verification of the relapse. Patients who relapse are considered off protocol but should be followed up, if possible, with reporting on the CR-05 Off Therapy Follow Up form.

1. Date of relapse/progression:

Date ___/___/_____ (dd/mm/yyyy)

2. Relapse site: (*Check <u>all</u> that are applicable)*

a. Right eye /orbit _____
b. Left eye /orbit _____
c. Bone marrow _____
d. CNS _____
e. Lymph node _____
f. CSF _____
g. Bone _____
h. Other sites; specify: _____

3. Did the patient complete all the 'first line' recommended therapy?

Yes _____ No _____

3.1 If yes, which of the following therapy did the patient receive? (Check all that are applicable)

3.1.1 Focal therapy _____
3.1.2 Surgery _____
3.1.3 Systemic chemotherapy _____
3.1.4 Intravitreal chemotherapy _____
3.1.5 Intra-arterial chemotherapy _____
3.1.6 Radiotherapy _____

3.2 If no, fill the abandonment form (CRF#07)

4. How was relapse treated?

____ With curative Rx

Specify details_____

____ With palliative Rx

Specify details: _____

RB-CRF 08 Abandonment Reporting Form

This form must be completed for all patients who fail to complete planned treatment.

1. Did the patient complete treatment?

    1.1 Yes____ No____

    1.2 If yes, check all that are applicable:

    Chemotherapy____

    Surgery: _____

    Focal therapy____

    Radiotherapy____

2. Was Complete Remission (CR) achieved?

    Yes____No____

    2.1 If yes, date of remission ___/___/_____ (dd/mm/yyyy)

    2.2 If No, why not:

    2.2.1 Abandonment of therapy ____

    If abandoned therapy, then answer the following:

    Date last seen in health facility _____ (dd/mm/yyyy)

3. Treatment phase when lost to follow up:

    a. Chemotherapy:

    Before Chemo ____ During Chemo ____ After Chemo completion____

    b. Surgery

    Before surgery ____ After surgery____

    c. Focal therapy

    Before focal therapy ____ During focal therapy____ After completion of focal therapy____

    d. Radiotherapy

    Before RT____ During RT____ After completion of RT____

4. Reason for Abandonment

    a. refused treatment _____

    b. social/ financial issues _____

    c. others _____

5. If died, fill death reporting form CRF08

RB-CRF 09 Death Reporting Form

This form must be completed for all patients who have confirmation of death (unilateral /bilateral and non-metastatic /metastatic RB). This must be filled immediately after verification of the death. All effort should be made to determine as exact a date of death as possible, for patients who die outside the hospital. Patients who are sent home on terminal care should have a telephone contact made to confirm the date of death.

1. Date of death? date ___/___/_____ (dd/mm/yyyy)
2. Where did the patient die?

   ____ Primary hospital (the hospital where the patient is registered on the study from)
   ____ Other hospital
   ____ At home
   ____ Other; specify: _____
3. What was the cause of death?

   ____ Disease Progression
   ____ Infection
   ____ Relapse
   ____ Treatment related toxicity; specify: _____
   ____ Second Malignant Neoplasm (SMN)
   ____ Other; specify:

   _____
   ____ Unknown