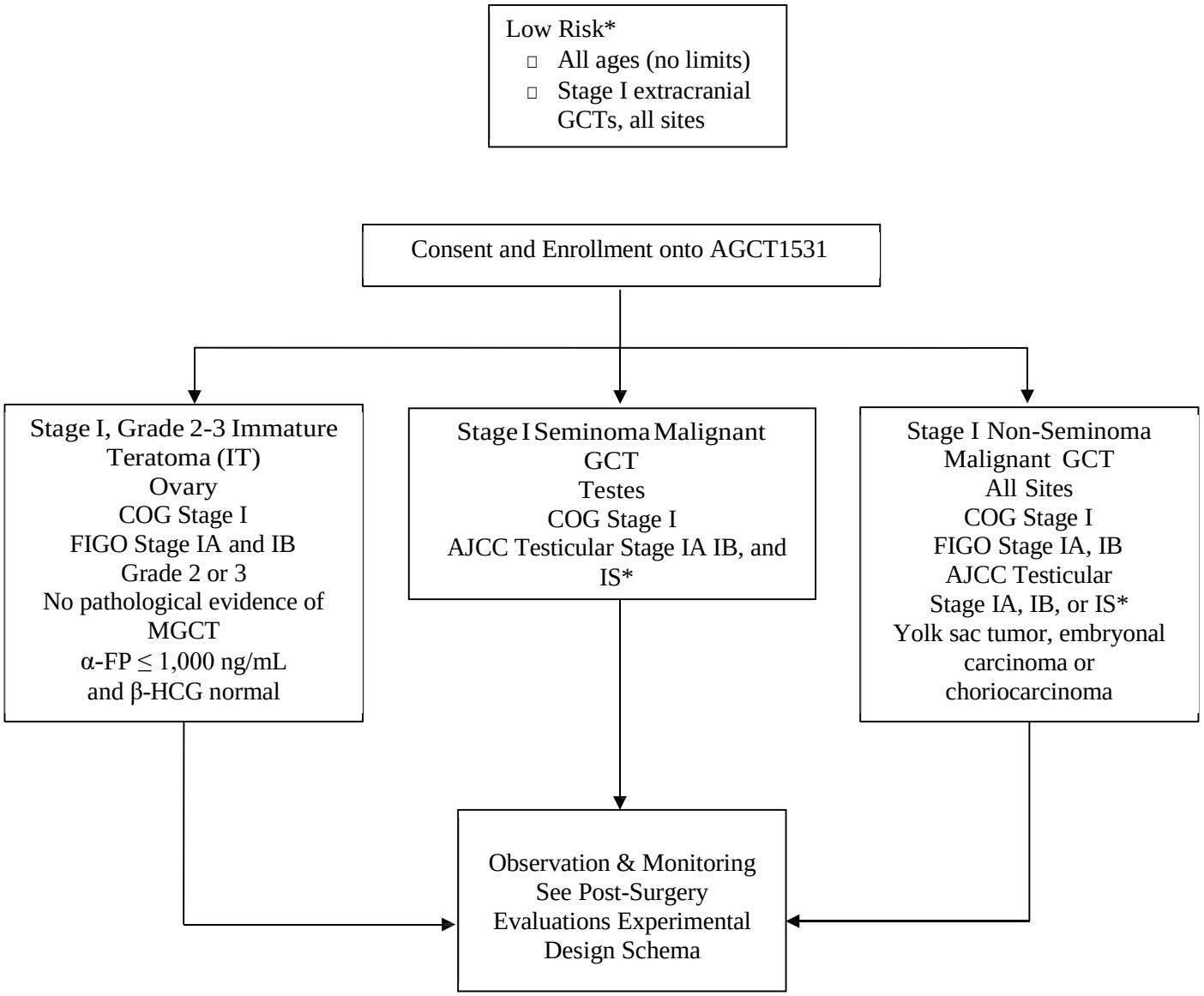
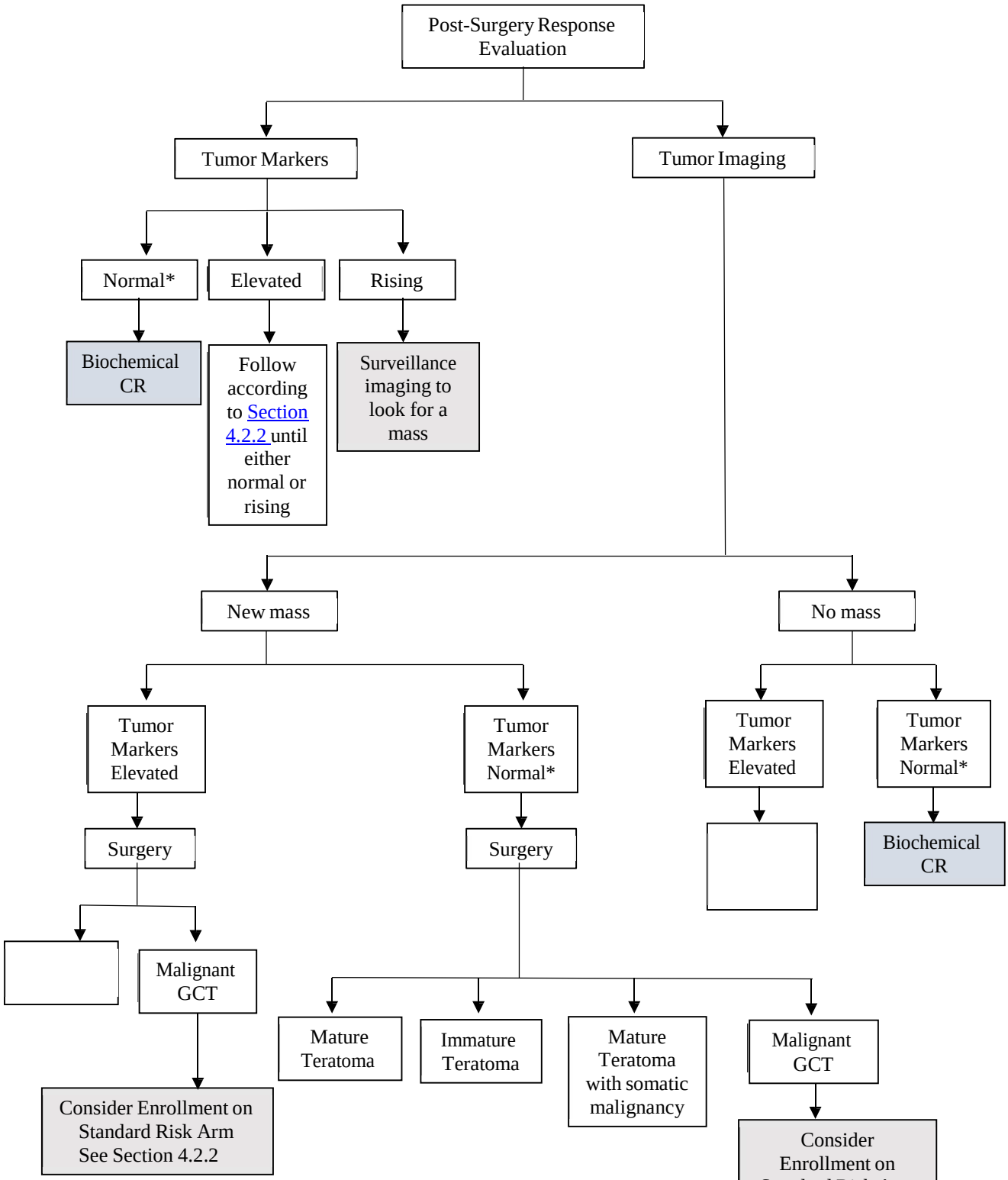
EXPERIMENTAL DESIGN SCHEMA: LOW RISK (LR)



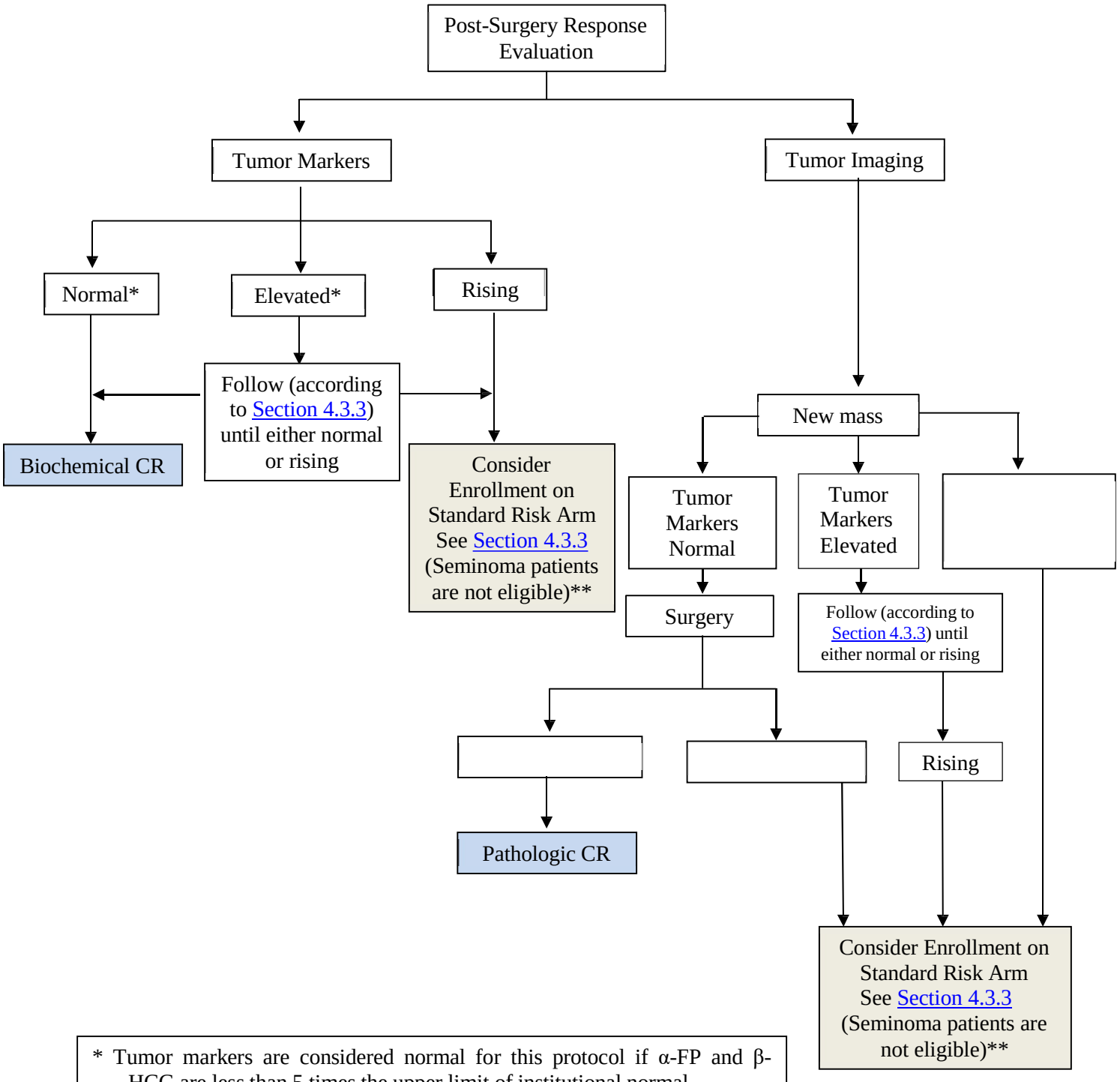
*Post-op tumor markers need to be lower (falling) compared to pre-op tumor markers.
Note: IGCCC criteria DO NOT apply to Low Risk/Stage I patients

EXPERIMENTAL DESIGN SCHEMA: POST-SURGERY EVALUATIONS FOR STAGE I GRADE 2, 3 OVARIAN IMMATURE TERATOMA



* Tumor markers are considered normal for this protocol if α-FP and β-HCG are less than 5 times the upper limit of institutional normal.

EXPERIMENTAL DESIGN SCHEMA: POST-SURGERY EVALUATIONS FOR STAGE I MALIGNANT GCT (SEMINOMA AND NON-SEMINOMA)



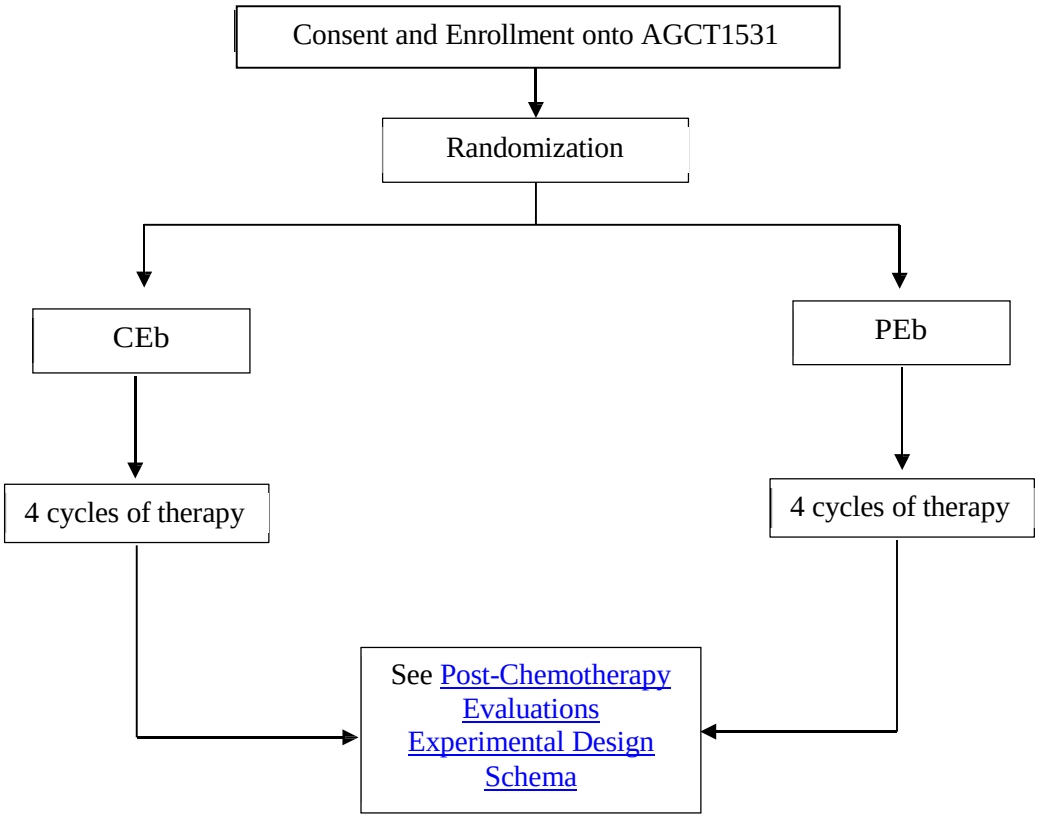
* Tumor markers are considered normal for this protocol if α-FP and β-HCG are less than 5 times the upper limit of institutional normal.

** If there is evidence of recurrence, seminoma patients are not eligible for the SR arms and should be treated at the discretion of the treating physician.

EXPERIMENTAL DESIGN SCHEMA: STANDARD RISK 1 (SR1)

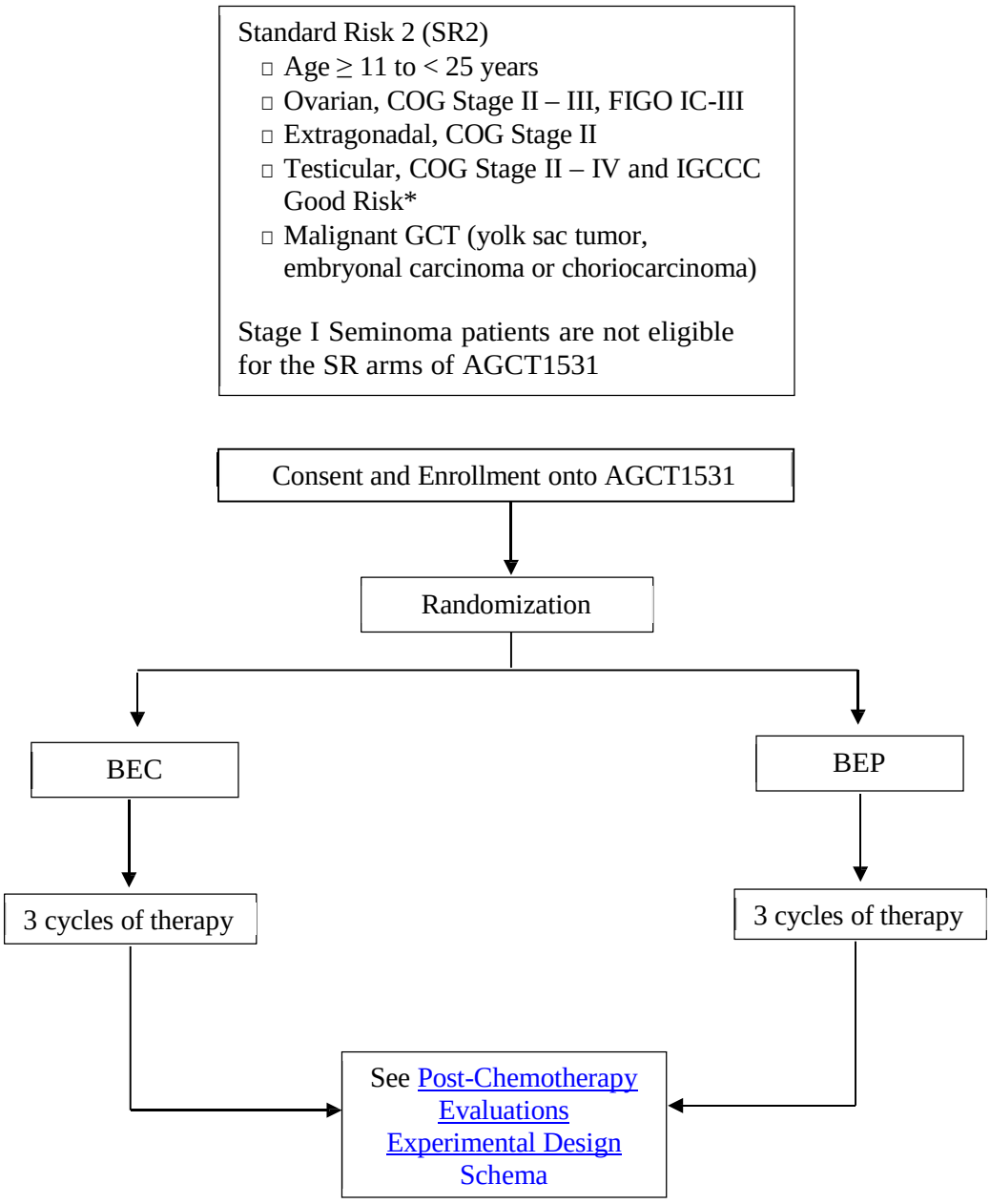
Standard Risk 1 (SR1)
- Age 0 < 11 years
- Stage COG II - IV extracranial GCTs, all sites
- Malignant GCT (yolk sac tumor, embryonal carcinoma or choriocarcinoma)
- IGCCC criteria DO NOT APPLY to SR1 patients

Stage I Seminoma patients are not eligible for the SR arms of AGCT1531



C = CARBOplatin
P = CISplatin
E = Etoposide
b = Bleomycin

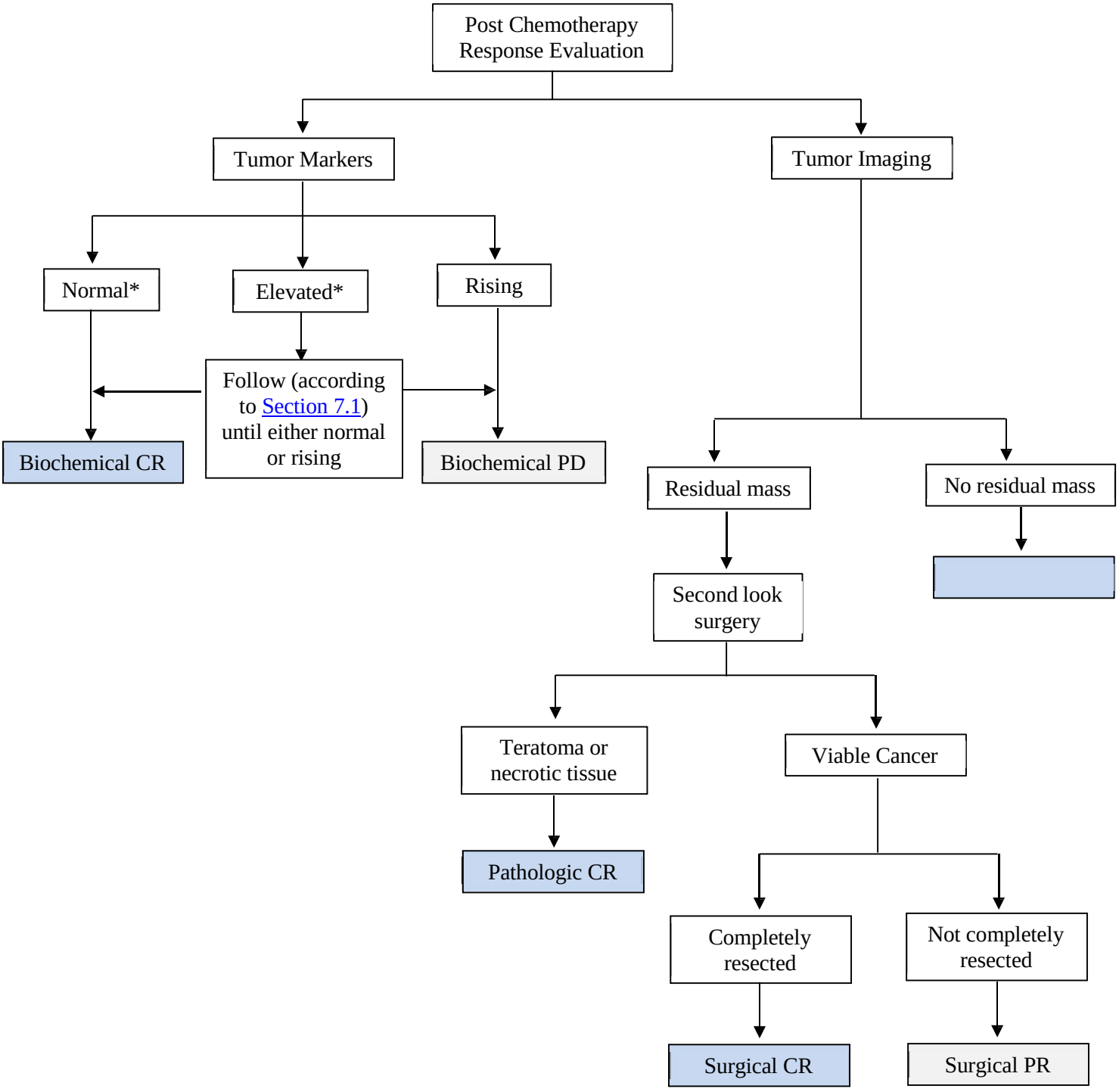
EXPERIMENTAL DESIGN SCHEMA: STANDARD RISK 2 (SR2)



B = Bleomycin
E = Etoposide
C = CARBOplatin
P = CISplatin

*IGCCC: Use post-op tumor marker levels to determine IGCCC risk category. IGCCC criteria apply ONLY to patients with a testicular primary tumor.

EXPERIMENTAL DESIGN SCHEMA: POST-CHEMOTHERAPY EVALUATIONS



* Tumor markers are considered normal for this protocol if α-FP and β-HCG are less than 5 times the upper limit of institutional normal.

3.2 Patient Eligibility Criteria

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

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are > 7 days old, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. The recommended imaging studies should be obtained within 8 weeks prior to enrollment for Low Risk patients, and within 14 days prior to enrollment for Standard Risk patients (clinical judgement should be used to determine if repeating the tumor imaging is necessary).

See Section 4.0 for required studies to be obtained prior to starting protocol therapy.

3.2.1 Age

3.2.1.1 There is no age limit for the Low Risk Stratum (Stage I Ovarian Immature Teratoma and Stage I Non-Seminoma or Seminoma Malignant GCT (all sites))

3.2.1.2 Standard Risk 1

Patients must be < 11 years of age at enrollment.

3.2.1.3 Standard Risk 2

Patients must be ≥ 11 and < 25 years of age at enrollment.

3.2.2 Diagnosis

Patients enrolling on one of the Low Risk arms must be newly diagnosed with a Stage I germ cell tumor. For the Standard Risk arms, patients must be newly diagnosed with metastatic germ cell tumor (Stage II or higher).

Histologic confirmation of a primary extracranial germ cell tumor in any of the categories outlined in the table below is required of all patients at enrollment except for those who were initially diagnosed with Stage I non-seminoma malignant GCT and later recur during observation post surgery off study (see Section 3.1.4). For these patients, if elevated tumor markers rise to > 5x ULN on at least 2 measurements taken at least 1 week apart, a diagnostic biopsy is not required for enrollment. Please refer to Section 4.2.2 (for immature teratoma) and Section 4.3.3 (for non-seminomatous malignant GCT) for complete details.

For COG, FIGO, AJCC and IGCCC staging criteria see Appendix II, Appendix III, Appendix IV and Appendix V, respectively.

NOTE: for low risk patients, materials for rapid surgical central review must be sent within 72 hours of study enrollment. See Section 3.1.6.

Diagnosis	Site	Stage	Grade	Histology	Tumor Markers	Age (years)
Low Risk Stage I Immature Teratoma (IT)	Ovarian	COG Stage I FIGO Stage IA and IB	2 or 3	Pure immature teratoma (may contain microscopic foci of yolk sac tumor) Mixed immature and mature teratoma (no pathological evidence of MGCT)	α-FP ≤ 1,000 ng/mL β-HCG institutional normal	All ages
Low Risk Stage I Non-Seminoma MGCT	Ovarian, Testicular, or Extragonadal	COG Stage I FIGO Stage IA and IB AJCC Testicular Stage IA IB, and IS		Must contain at least one of the following: □ yolk sac tumor (see notes), □ embryonal carcinoma, or □ choriocarcinoma (pure or mixed)	N/A	All ages
Low Risk Stage I Seminoma-MGCT	Testicular	COG Stage I AJCC Testicular Stage IA IB, and IS		May contain □ immature/mature teratoma May NOT contain □ yolk sac tumor, □ embryonal carcinoma, or choriocarcinoma	N/A	All ages
Standard Risk 1 (SR1)	Ovarian, Testicular, or Extragonadal	COG Stage II – IV FIGO Stage IC, FIGO Stages II – IV (IGCCC criteria DO NOT apply)		Must contain at least one of the following: □ yolk sac tumor (see notes), □ embryonal carcinoma, or □ choriocarcinoma	N/A	< 11
Standard Risk 2 (SR2)	Ovarian	COG Stage II and III FIGO Stage IC, II and III		Must contain at least one of the following: □ yolk sac tumor (see notes), □ embryonal carcinoma, or □ choriocarcinoma	N/A	≥ 11 and < 25
	Testicular	COG Stage II - IV AJCC Stage II, III and IGCCC Good Risk (See Appendix V)		Must contain at least one of the following: □ yolk sac tumor (see notes), □ embryonal carcinoma, or □ choriocarcinoma	Must be IGCCC Good Risk. Post op: α-FP < 1,000 ng/mL β-HCG < 5,000 mIU/mL and LDH < 3.0 x normal	
	Extragonadal	COG Stage II		Must contain at least one of the following: □ yolk sac tumor (see notes), □ embryonal carcinoma, or □ choriocarcinoma	N/A	

Notes:

- **IGCCC criteria only apply to SR2 patients with a testicular primary tumor.**
- **Use post-op tumor marker levels to determine IGCCC risk group.**
- **Stage 1 seminoma patients are not eligible for the Standard Risk arms of the study.**

□ For the Low Risk Stage I Non-Seminoma MGCT and the Standard Risk arms, components of yolk sac tumor, embryonal carcinoma, or choriocarcinoma can be mixed with other forms of GCT, such as seminoma or mature or immature teratoma. If yolk sac tumor is the only malignant component present, then it must be deemed by the pathologist to be greater than a "microscopic component" of yolk sac tumor.

3.2.3 Performance Level

Patients must have a performance status corresponding to ECOG scores of 0, 1, 2 or 3. Use Karnofsky for patients > 16 years of age and Lansky for patients □ 16 years of age (see Appendix VI).

3.2.4 Organ Function Requirements

Organ function requirements apply ONLY to patients who will receive chemotherapy (SR1 and SR2 patients).

3.2.4.1 Adequate renal function defined as:

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

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

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR[60] utilizing child length and stature data published by the CDC.

3.2.4.2 Adequate liver function defined as:

- Total bilirubin 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 2.5 x upper limit of normal (ULN) for age (for the purpose of this study, the ULN for SGPT is 45 U/L).

3.2.4.3 Adequate Hematological Function defined as:

- Peripheral absolute neutrophil count (ANC) 1,000/mm^3, and
- Platelet count 100,000/mm^3

3.2.5 Patients enrolling on the standard risk arms must be medically fit to receive protocol treatment and with no contraindications to protocol treatment.

3.2.6 Exclusion Criteria

3.2.6.1 Patients with any diagnoses not listed in the table in Section 3.2.2 including:

- Stage I testicular cancer patients who have undergone primary RPLND (retroperitoneal lymph node dissection),
- Pure dysgerminoma
- Pure mature teratoma,
- Pure immature teratoma COG Stage I, Grade I
- Pure immature teratoma COG Stage I, Grade 2, 3 with AFP ≥ 1000 ng/mL,
- Pure immature teratoma COG Stage II - IV or FIGO Stage IC to IV,
- "Poor risk" GCT [age ≥ 11 years old and COG Stage IV ovarian, COG Stage III or IV EG, or IGCCC intermediate or poor risk testicular (see Appendix V)], or

- Primary CNS germ cell tumor.
- Germ cell tumor with somatic malignant transformation
- Spermatocytic seminoma

3.2.6.2 Patients must have had no prior systemic therapy for the current cancer diagnosis.

3.2.6.3 Patients must have had no prior radiation therapy with the exception of CNS irradiation of brain metastases. [This exception only applies to SR1 patients; any patients over age 11 with distant metastases to brain (Stage IV disease) would be considered poor risk and therefore not eligible for this trial.]

3.2.6.4 Patients with significant, pre-existing co-morbid respiratory disease that contraindicate the use of bleomycin, are ineligible for the standard risk arms of the trial.

3.2.6.5 Pregnancy and Breast Feeding
These criteria apply ONLY to patients who will receive chemotherapy (SR1 and SR2 patients).

3.2.6.5.1 Female patients who are pregnant since fetal toxicities and teratogenic effects have been noted for several of the study drugs. A pregnancy test is required for female patients of childbearing potential.

3.2.6.5.2 Lactating females who plan to breastfeed their infants.

3.2.6.5.3 Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation.

3.2.7 Eligibility Criteria to Participate in the Pilot Study of the AYA-Hears Instrument (PROs of Ototoxicity)

Note: participants in Group 1 will not receive AGCT1531 protocol-directed therapy and therefore the above eligibility/exclusion criteria do not apply. See Section 16.2 for more details. All other AYA-HEARS patients must be enrolled on the AGCT1531 SR2 arm in order to participate.

- ≥ 11 and < 25 years old at enrollment
- Able to fluently speak and read English
- Has received prior cisplatin- or carboplatin-based chemotherapy regimen for malignancy including diagnoses other than germ cell tumor
- Followed for cancer or survivorship care at one of the following institutions:
    - Baylor College of Medicine/Dan L Duncan Comprehensive Cancer Center
    - Dana Farber/ Harvard Cancer Center
        - Hospital for Sick Children
    - Children's Hospital of Eastern Ontario
    - Oregon Health and Science University
    - Seattle Children's Hospital
        - Yale University

3.2.8 Regulatory Requirements

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

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