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Participating Institution(s): WFBCCC

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Confidentia

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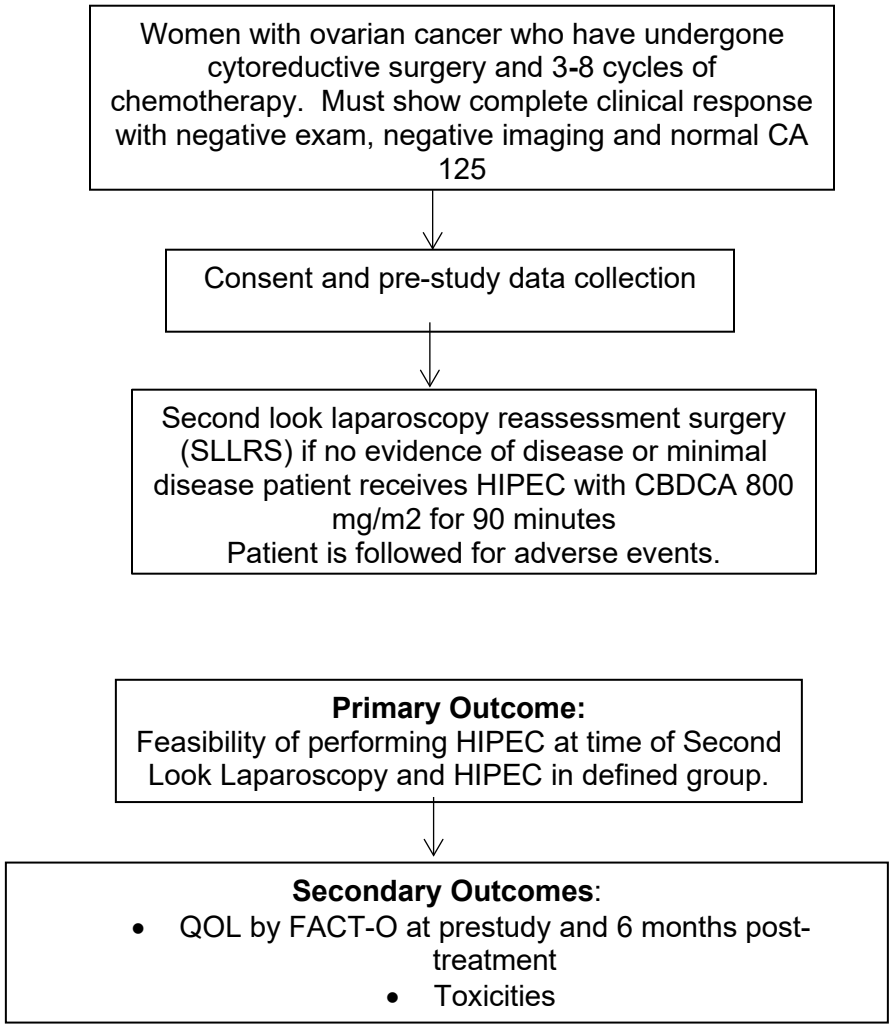
SCHEMA


Women with ovarian cancer who have undergone cytoreductive surgery and 3-8 cycles of chemotherapy. Must show complete clinical response with negative exam, negative imaging and normal CA 125
Consent and pre-study data collection
Second look laparoscopy reassessment surgery (SLLRS) if no evidence of disease or minimal disease patient receives HIPEC with CBDCA 800 mg/m2 for 90 minutes
Patient is followed for adverse events.
Primary Outcome:
Feasibility of performing HIPEC at time of Second Look Laparoscopy and HIPEC in defined group.
Secondary Outcomes:
QOL by FACT-O at prestudy and 6 months post-treatment
Toxicities

1.0 Introduction and Background

Ovarian Cancer

Ovarian, fallopian tube, primary peritoneal cancer (noted generically below as ovarian cancer) is the twelfth leading cause of cancer death in the United States. Less than 15% of patients are diagnosed at the local stage; for 61%, the cancer has metastasized. For these patients, 5-year survival rates are a dismal 27% [1].

Cytoreductive Surgery

The standard treatment for women presenting with advanced-stage ovarian cancer is surgical cytoreduction (CRS) followed by platinum-based chemotherapy agents[2].

Second Look Laparoscopy

Second look laparoscopy (SLL) was first introduced in the 1950s to access the status of intra-abdominal disease in colon cancer. The procedure was then applied to other intra-abdominal malignancies including ovarian cancer. It was used initially as a diagnostic tool because it was the most accurate in determining persistent disease after systemic chemotherapy. Long-term survival has been shown to be favorable in patients with histologically negative SLL; however, the recurrence rates in this group approached 50%[3, 4].

In patients with advanced disease, who undergo cytoreduction and systemic chemotherapy and have no clinical evidence of disease, second look procedures reveal that approximately 50% have residual disease. Of these patients about 50% have macroscopic disease and 50% microscopic disease. Even among patients who undergo second look procedures and show no obvious signs of persistent disease, approximately 50% experience a subsequent recurrence.

Problems associated with second look laparoscopy and utilization of consolidation therapy are related to the fact that there is no evidence of survival benefit [5]

Because clinical measures including imaging and tumor marker analysis can appear negative even in the presence of macroscopic or microscopic disease, second look laparoscopy offers an opportunity for physicians to act upon residual cancer before it becomes widespread.

HIPEC

Hyperthermic intraperitoneal chemotherapy (HIPEC) is based on the rationale that intraperitoneal chemotherapy has a substantial pharmacokinetic advantage over systemic chemotherapy. The hyperthermia effects cell membranes, cytoskeletons, synthesis of macromolecules and DNA repair mechanisms.[6] [7] Furthermore, mild hyperthermia has been shown to potentiate the anti-tumor effects of oxaliplatin, mitomycin C (MMC), and cisplatin[8-11]. The MTD for carboplatin has been established at 1000 mg/m^2 for 90 minutes. This Phase 1 study was mainly in patients who are chemotherapy naïve[12]. While hyperthermia has some cytostatic properties, it is the synergetic effect on chemotherapeutic agents which has lead most centers to utilize hyperthermia with chemoperfusion. The primary objective of HIPEC is to maximize drug-tumor interaction while minimizing systemic toxicity.

The timing of peritoneal perfusion is critically important. Extensive evidence shows that the effect of postoperative HIPEC is reduced due to the rapid formation of intra-abdominal adhesions, as well as, complications related to intra-abdominal catheters.[13-15] The current study proposes to evaluate the feasibility of administering peritoneal perfusion intraoperatively. Intraoperative peritoneal perfusion not only allows for the instillation of chemotherapeutic agents in an adhesion-free environment, it also minimizes the number of viable exfoliated tumor cells after resection.[16-18] Taken together, this represents the biologic foundation for the current use of HIPEC in the treatment of advanced ovarian malignancies.

HIPEC in epithelial ovarian carcinoma, fallopian tube carcinoma and primary peritoneal carcinoma is potentially beneficial recognizing the disease history of intraperitoneal involvement without extraperitoneal metastasis for an extended period of time. It is recognized that direct chemotherapy administration–peritoneal therapy would be of benefit only in situations in which there was microscopic or minimal visible (gross) disease with limited direct chemotherapy penetration although it is appreciated that peritoneal absorption of chemotherapy into the bloodstream does provide some secondary tumor cell exposure.

There is data now supporting the incorporation of HIPEC in the treatment of ovarian carcinoma[19, 20].

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 Determine the feasibility of second look laparoscopy and HIPEC with carboplatin.

2.2 Secondary Objective(s)

2.2.1 To compare the QOL in patients with ovarian cancer after undergoing second look laparoscopic reassessment surgery with HIPEC using carboplatin (CBDCA) versus QOL in patients treated with CRS and systemic chemotherapy alone [21].

2.2.2 To describe toxicities in patients with ovarian cancer treated with SLL and simultaneous HIPEC.

3.0 Patient Selection

3.1 Inclusion Criteria

3.1.1 Patients must have histologically I-III epithelial carcinoma of the ovary, fallopian tube or peritoneum or stage IVA disease in which there is complete resolution of disease (pleural effusion) with chemotherapy.

3.1.2 Patients must have undergone cytoreductive surgery and 3-8 cycles of platinum-based systemic chemotherapy prior to the second look surgery. Systemic platinum based chemotherapy must be completed <18 weeks prior to second look surgery.

3.1.3 Cytoreductive surgery must result in an R-0, R-1 resection prior to systemic chemotherapy

3.1.4 The intraoperative peritoneal adhesion index should be ≤ 10.[22] (See appendix)

3.1.5 Patients must be without clinical evidence of disease including a negative exam, imaging (CT or PET/CT) and normal tumor markers (CA125) after completion of systemic chemotherapy.

3.1.6 Age ≥ 18 years.

3.1.7 ECOG performance status ≤ 2.

3.1.8 Patients must have adequate organ and marrow function as defined below (within 30 days of registration):

- absolute neutrophil count >1,500/mcL
- platelets >100,000/mcL
- total bilirubin ≤ 1.5 mg/dL
- creatinine clearance ≥ 50 mg/dL
- AST(SGOT)/ALT(SGPT) ≤ 3 X institutional upper limit of normal
- alkaline phosphatase ≤ 3 X institutional upper limit of normal

3.1.9 Adequate contraception and negative pregnancy test if pregnancy possible.

3.1.10 Ability to understand and the willingness to sign an IRB-approved informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients greater than 18 weeks from their last course of systemic platinum based chemotherapy

3.2.2 Patients who have received additional chemotherapy for the ovarian cancer after primary therapy as outlined above.

3.2.3 Patients may not have received prior abdominal or pelvic radiation.

3.2.4 Extensive intra-abdominal adhesive disease noted at the time of initial cytoreductive surgery with PAI of >10 as defined above

3.2.5 Intra-abdominal infection associated with initial cytoreductive surgery requiring extended hospitalization or related to systemic chemotherapy requiring hospitalization for therapy

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to carboplatin.

3.2.7 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnancy

3.2.9 Men are excluded from participation due to the site-specific nature of the disease being studied.

3.3 Inclusion of Women and Minorities

Women of all races and ethnicity who meet the above-described eligibility criteria are eligible for this trial. Men are excluded from participation due to the site-specific nature of the disease being studied.

4 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked with a protocol in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix B)
2. Complete the Protocol Registration Form (Appendix A)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The primary outcome is feasibility. The proportion of feasibility is defined as the number of patients who successfully undergo SLL and HIPEC divided by the number of patients who are eligible and consent to participate. It is anticipated that greater than or equal to 75% of patients eligible and consented will complete SLL and HIPEC. This is based on the personal experience of the PI who has performed in the past a significant number of second look procedures that were inclusive of the laparoscopic approach. In addition, the PI has experience with HIPEC procedures.

- Extraperitoneal disease noted at the time of the second look procedure
- Macroscopic intraperitoneal disease which is not resectable to R1
- Technical problems which prevent continuous, adequate flow to maintain intraperitoneal temperature to 41°C during perfusion
- Intraoperative complications such as cardiac or pulmonary instability precluding HIPEC

5.2 Secondary Outcomes

5.2.1 QOL in patients with advanced ovarian cancer treated with CRS, systemic chemotherapy and SLL with HIPEC as determined by the FACT-O questionnaire 3 and 6 months post-treatment

5.2.2 Toxicities in patients with advanced ovarian cancer who receive a SLL procedure with HIPEC after their standard CRS and chemotherapy regimen. Toxicities will be indicated by the number and severity of adverse events as defined by CTCAE v5.0

6.0 Intervention Plan

6.1 Study-Related Interventions

	Pre-Study [a]	Day of Procedure	Daily, Post op days while in hospital	2 weeks	6 weeks	3 months	6 months
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent meds	X						
Height, Weight, BSA	X	X		X	X	X	X
Op Note, Path Report, Perfusion Flowsheet		X					
Adverse event evaluation		X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X
Performance Status (ECOG)	X	X	X	X	X	X	X
B-HCG	X						
CBC w/diff, plts	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X
CA-125	X						
CT of chest, abdomen,pelvis	X						
FACT-O, questionnaires	X					X	X

a: all pre-study procedures should occur within 28 days prior to registration

6.2 Treatment Administration: During second look laparoscopy

Adverse events and potential risks are described in Section 8.0 No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

HIPEC			
Intervention	**Dose**	**Route**	**Schedule**
SLL			< 18 weeks after IV chemotherapy cycles are completed
Carboplatin	800 mg/m^2	IP over 90 minutes	During SLL procedure

6.2.1 Surgical Intervention and HIPEC

6.2.1.1 Second Look laparoscopy

Patients will have a mechanical and antibiotic bowel preparation. Standard surgical antibiotic prophylaxis will be used.

Laparoscopic assessment of disease status and resection as feasible. The goal is adequate assessment of the peritoneal cavity with lysis of adhesions as necessary, noting either no gross residual disease or minimal residual disease prior to or after resection. This performed prior to establishment of a peritoneal perfusion circuit and HIPEC.

6.2.1.2 HIPEC

Patients will be cooled to a core temperature of about 34 to 35° C by passive measures (i.e., not warming airway gases or intravenous solutions). After the completion of SLL, peritoneal perfusion catheters will be placed percutaneously and directed laparoscopically. Two inflow catheters (22Fr) will be directed beneath the left and right hemidiaphragms. One or two outflow catheters (32Fr) will be placed in the pelvis. Intraperitoneal catheters will be placed as per institutional standard practice. Temperature probes will then be placed on the inflow and outflow catheters. The abdominal skin incision will be temporarily closed with a running suture to prevent leakage of peritoneal perfusate. A perfusion circuit will be established with 3 L of crystalloid perfusate solution, such as sodium chloride, Lactated Ringers or Plasmalyte. If a perfusion circuit cannot be established with 3 liters a 4th liter is acceptable, but under no circumstances should the volume of perfusate be greater than 4 liters. Flow rates should be at least one liter per minute. The pelvic catheters will drain to a reservoir containing a coarse filter for debris and to reduce foaming. The heated chemotherapy solution will be added and circulated through the

institution's standard perfusion equipment. The temperature of the fluid in the patient-return and patient-directed tubing will be monitored using stainless steel couplers with temperature probe connectors and needle probes at the tips of one inflow and one outflow cannula. The abdomen will be gently massaged throughout the perfusion to improve drug distribution to all peritoneal surfaces. Constant temperature monitoring will be done at all temperature probes. A perfusion record will be completed during HIPEC (see Forms). Following the perfusion, the peritoneum will be washed out with 3 liters of the crystalloid perfusate.

HIPEC Chemotherapy Administration

Carboplatin will be added to the perfusate once outflow temperatures reach 40° C at a dose of 800 mg/m^2. This dose reduction from 1000 mg/m² will be used since patients have been previously treated with systemic chemotherapy. In addition, in a prior phase 1 study 800 mg/m² was an established dose of carboplatin for HIPEC [23] A maximum inflow temperature of 42.5°C is tolerated during the perfusion. The target outflow temperature is 40°C. Flow rate will be approximately 800 to 1000 mL/min. The total perfusion time after the initial addition of carboplatin will be 90 minutes. The carboplatin dose will be calculated based on the body surface area noted on admission (or as close to surgery day as possible). Following the perfusion, the peritoneum will be washed out with 3 liters of perfusate and passively drained. The skin will then be opened, and the cannulas removed under direct vision. If a bowel resection is performed, any anastomoses may be completed before or after HIPEC; ostomies will be completed at the end of the entire procedure. The abdomen will be inspected and the required anastomoses will be created. The fascia and skin will then be closed in a standard fashion and the requisite ostomies will be created if necessary.

Patients who exhibit the following will not receive the HIPEC procedure:

- Extraperitoneal disease noted at the time of the second look procedure
- Macroscopic intraperitoneal disease which is not resectable to R1
- Technical problems which prevent continuous, adequate flow to maintain intraperitoneal temperature to 41°C during perfusion
- Intraoperative complications such as cardiac or pulmonary instability precluding HIPEC

6.2.1.3 Postoperative Care

The patient will be transferred to the post-anesthesia care unit for aftercare and then to the intensive care unit, if needed. Early and late complications of surgery will be recorded in the patient's research chart. Adverse event monitoring will begin 24 hours after the end of surgery and will continue until 3 months post-op.

6.3 General Concomitant Medication and Supportive Care Guidelines

Patients should receive *full supportive care*, including transfusions of blood and blood products, erythropoietin, neupogen, antibiotics, antiemetics, etc., as clinically indicated. Anti-inflammatory or narcotic analgesics may be offered as needed. Medications considered necessary for the patient's well-being may be given at the discretion of the investigator, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc. The reason(s) for treatment, dosage, and dates of treatment should be recorded on the flow sheets.

6.4 Duration of Intervention and Follow Up

The study intends to evaluate the feasibility quality of life of SLL with HIPEC. Patients will participate in the surgical procedure and then attend follow up visits for up to 6 months.

6.5 Criteria for Removal from Study

Patients may withdraw/be withdrawn from the trial at any time and for any reason. Patients will not be replaced. Some possible reasons for early withdrawal include the following:

- Development of an intercurrent medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
  Extraperitoneal disease noted at the time of the second look procedure
  - Macroscopic intraperitoneal disease which is not resectable to R1
  - Technical problems which prevent continuous, adequate flow to maintain intraperitoneal temperature to 41°C during perfusion
  - Intraoperative complications such as cardiac or pulmonary instability precluding HIPEC
- Study completion or discontinuation
- Patient withdraws consent to continued participation in the trial

The reason and date of discontinuation are to be documented in the patient's medical record and in the CRF.

The investigator should complete all end of treatment procedures when a patient withdraws from treatment. All patients who discontinue the trial secondary to an adverse event should be followed until resolution, stabilization or return to a baseline condition. All patients who undergo HIPEC with study agents will be included in any safety analysis.

The Co-Principal Investigators may discontinue the trial at any time. Reasons for early trial discontinuation may include, but are not limited to, unacceptable toxicity of study treatment, a request to discontinue the trial from a regulatory authority or an IRB, or poor enrollment.

7.0 Measurement of Effect

7.1 Definitions

Evaluable for toxicity. All patients who have Second Look Laparoscopy with HIPEC

Moran-Janet Hematologic toxicities will be recorded in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

7.2 Methods for Evaluation of Quality of Life

Patients' QOL, neurological symptoms and abdominal discomfort will be assessed with patient self-administered questionnaires.

7.2.1 Quality of Life

Patient reported outcomes will be assessed at seven-time points:
1) Pre-Study
2) At baseline 3 months, 6 months,

QOL will be measured using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire. The FACT-O is a multidimensional QOL questionnaire developed and validated for use by ovarian cancer patients; it includes 4 subscales: Physical Well-Being (7 items), Social Well-being (7 items), Functional Well-Being (7 items), Emotional Well-Being (6 items) and Additional Ovarian Cancer Concerns (12-items). These subscales can be analyzed separately or aggregated to produce a total score. The FACT-O has demonstrated reliability, validity, and responsiveness to change over time 31 as well as sensitivity to improvements in QOL experienced by patients responding to platinum/taxane therapy.

8.0 Adverse Events List and Reporting Requirements

8.1 Adverse Event List

8.1.2 Carboplatin

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values†
Bone Marrow				
Thrombocytopenia	<100,000/mm3	59	35	< 0.001
	<50,000/mm3	22	11	0.006
Neutropenia	<2,000 cells/mm3	95	97	ns
	<1,000 cells/mm3	84	78	ns
Leukopenia	<4,000 cells/mm3	97	97	ns
	<2,000 cells/mm3	76	67	ns
Anemia	<11 g/dL	88	87	ns
	<8 g/dL	8	24	< 0.001
Infections		18	21	ns
Bleeding		6	4	ns
Transfusions		25	33	ns
Gastrointestinal				
Nausea and vomiting		94	96	ns
Vomiting		82	91	0.007
Other GI side effects		40	48	ns
Neurologic				
Peripheral neuropathies		13	28	0.001
Ototoxicity		12	30	< 0.001
Other sensory side effects		4	6	ns
Central neurotoxicity		23	29	ns
Renal				
Serum creatinine elevations		7	38	< 0.001
Blood urea elevations		-	-	-
Hepatic				
Bilirubin elevations		5	3	ns
SGOT elevations		23	16	ns
Alkaline phosphatase elevations		29	20	ns
Electrolytes loss				

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		Carboplatin Arm Percent*	Cisplatin Arm Percent*	P-Values†
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	< 0.001
Other side effects				
Pain		54	52	ns
Asthenia		43	46	ns
Cardiovascular		23	30	ns
Respiratory		12	11	ns
Allergic		10	11	ns
Genitourinary		11	13	ns
Alopecia ‡		43	57	0.009
Mucositis		6	11	ns
*Values are in percent of evaluable patients †ns = not significant, p > 0.05 ‡May have been affected by cyclophosphamide dosage delivered				

8.1.3 HIPEC

8.1.3.1 Intraoperative and postoperative hyperthermia has not shown significant complications with the close monitoring and intraoperative cooling methods which are standard for HIPEC therapy.

8.1.3.2 Previous analysis revealed a risk of anastomotic bowel leaks of 8.7% with risk factors including preoperative functional status and number of anastomoses.[24] Patients in this protocol will not undergo bowel resection/anastomosis and HIPEC.

8.1.3.3 Also the previously cited reference[20] noted that there was no significant differences between the 2 groups in the incidence of adverse events of any grade. Adverse events of grade 3 or 4 were reported in approximately 25% of each group. (cytoreductive surgery without HIPEC versus cytoreductive surgery with HIPEC)

8.1.3.4 Among patients with stage III ovarian carcinoma the addition of HIPEC to interval cytoreductive surgery resulted in a longer recurrence free survival and overall survival than surgery alone and did not result in higher rates of side effects.[20]

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

- Definite – The AE **is clearly related** to the study treatment.
- Probable – The AE **is likely related** to the study treatment.
- Possible – The AE **may be related** to the study treatment.
- Unlikely – The AE **is doubtfully related** to the study treatment.
- Unrelated – The AE **is clearly NOT related** to the study treatment.

8.3 DSMC SAE Reporting Requirements

The Data and Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization > 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER. All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 9.1.

9.1 Pharmaceutical Accountability

Drug accountability logs will be maintained for all agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

9.2 Carboplatin

Product description: PARAPLATIN® (carboplatin) for Injection, USP is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intraperitoneal infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Solution preparation: Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D5W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL. PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection, USP.

Storage requirements: Unopened vials of PARAPLATIN are stable for the life indicated on the package when stored at 25°C (77°F); excursions permitted from 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Protect from light.

Stability: When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25°C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN solutions be discarded 8 hours after dilution.

Route of administration: PARAPLATIN will be administered adding to the intraperitoneal perfusate arriving from the chemotherapy pharmacy at the calculated dose in 500 mL of normal saline.

Disposal: Caution should be exercised in handling and preparing PARAPLATIN (carboplatin) for Injection, USP. Several guidelines on this subject have been published. To minimize the risk

of dermal exposure, always wear impervious gloves when handling vials containing PARAPLATIN (carboplatin) for Injection, USP. If PARAPLATIN (carboplatin) for Injection, USP or solutions containing PARAPLATIN (carboplatin) for Injection, USP contact the skin, immediately wash the skin thoroughly with soap and water. If PARAPLATIN (carboplatin) for Injection, USP or solutions containing PARAPLATIN (carboplatin) for Injection, USP contact mucous membranes, the membranes should be flushed immediately and thoroughly with water.

10.0 Correlative Studies

None

11.0 Data Management

The forms packet contains master copies of the case report forms (CRFs) to be used for this protocol.

Note: If the patient does not have protocol therapy at surgery, it is still necessary to submit Day 0 data and the No HIPEC Follow-Up form annually.

Informed consent document	EPIC
Protocol registration Form	WISER
FACT-O	WISER
Follow-up form	WISER
RECIST measurement form	WISER
Adverse Events Log	WISER
Vitals with Embedded ECOG Form	WISER
Pretoxicity	WISER
Demographics	WISER
NCI Comorbidities	WISER
Peritoneal Cancer Index form HIPEC	WISER
Surgery Form	WISER
Survival Form	WISER
Follow up Form	WISER
Off Treatment Study	WISER
Concomitant Medications	WISER
Solid Tumor Response	WISER
Medical History	WISER

The Protocol Registration Form and signed Informed Consent Form should be completed and faxed to the WFBCCC Registrar in order to enroll and randomize participants. All other CRFs & supporting documents should be faxed to the attention of the Study Coordinator according to the following schedule:

Form	**Submission Schedule**
Surgery Form	Form and reports within 30 days of surgery
Perfusion Record - HIPEC Form	Form within 30 days of surgery
Adverse Event Log	Form within 7 days of completion of surgery.
Follow up/Measurement Form and ECOG Form	Form and supporting documents Prestudy and within 7 days of month 3 and 6
FACT-O	Form-Pre-Study,3 months, 6 months
Extra data tracking questions have been added to the case report forms that may have relevance to the outcome of this study. These include tracking the length of surgery, length of hospital stay, blood products received within the 30 day post-op period and prior surgical score.	

12.0 Statistical Considerations

12.2 Analysis of Primary Objective

This is a descriptive study. The primary objective is to calculate the feasibility of intraoperative HIPEC at the time of SLL reassessment surgery. The feasibility proportion is calculated as the number of patients who can successfully complete the SLL surgery and HIPEC divided by those who consent to the study. The feasibility proportion and its 95% confidence interval will be estimated.

12.3 Analysis of Secondary Objective

There are two secondary objectives:

12.3.1 The QOL in patients with advanced ovarian cancer after undergoing SLL reassessment surgery with HIPEC using CBDCA will be determined by the FACT-O questionnaire at pre-study, and months 3, and 6 in follow-up (post-treatment). The distribution of QOL at each visit and the distribution of change in QOL at each follow-up visit will be examined and the descriptive statistics will be presented. In addition, the longitudinal data of QOL over time will be displayed graphically with individual trajectories. The summary statistics for the historical control data will be available from literature [16,17]. We do not have individual data for historical controls. We will compare the QOL at 3 and 6 months with patients treated with CRS and systemic chemotherapy alone (historical controls) using two sample t-test if mean and standard error are available from the literature or using one sample t-test if only mean QOL is available in the literature.

12.3.2 The toxicities will be measured by the number and severity of adverse events defined by CTCAE v5.0. Counts and percentages will be calculated for each adverse event. Mean, standard deviation, median, and interquartile range will be calculated for number of adverse events.

12.4 Power and Sample Size

This study is for descriptive purpose. The proportion of feasibility is unknown. The data collected in this study will be informative for future research. Based on the Principal Investigator's clinical experience, we anticipate greater than 75% of patients are able to undergo HIPEC and SLL in order for this study to be considered a success. Assuming the feasibility proportion is 0.75 and a sample size of 10, the 95% confidence interval for the feasibility proportion ranges from 0.48 to 1.00.

12.5 Estimated Accrual Rate

Accrual is expected to be 10 patients in 18 months. Targeted accrual should be met within 1 ½ years.

12.6 Estimated Study Length

The total study length is approximately 2 years.

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