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SUMMARY OF CHANGES

For Protocol Revision #5 to GOG-0275

NCI Protocol #: GOG-0275
Local Protocol #: GOG-0275

NCI Version Date: 03/25/2015
Protocol Date:

#	Section	Page(s)	Change
1.	Title Pages	1-3	• The NCI Version Date is now 03/25/2015. • Includes Revisions #1-5.
2.	11.32	40, 41	Accrual rates have been revised.
3.	11.33	41	This section has been expanded to include information regarding revised accrual rates.
4.	IC		The NCI Version Date is now 03/25/2015.

PROTOCOL GOG-0275

A PHASE III RANDOMIZED TRIAL OF PULSE ACTINOMYCIN-D VERSUS MULTI-DAY METHOTREXATE FOR THE TREATMENT OF LOW-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA NCT #01535053 **(11/24/2014)**

NCI Version Date 03/25/2015
Includes Revisions #1-5
POINTS:
PER CAPITA -20
MEMBERSHIP -6

Lead Organization: NRG / NRG Oncology (11/24/2014)

Participating Organizations (11/24/2014)
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

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PROTOCOL GOG-0275

A PHASE III RANDOMIZED TRIAL OF PULSE ACTINOMYCIN-D VERSUS MULTI-DAY METHOTREXATE FOR THE TREATMENT OF LOW-RISK GESTATIONAL TROPHOBLASTIC NEOPLASIA

NCI Version Date 03/25/2015

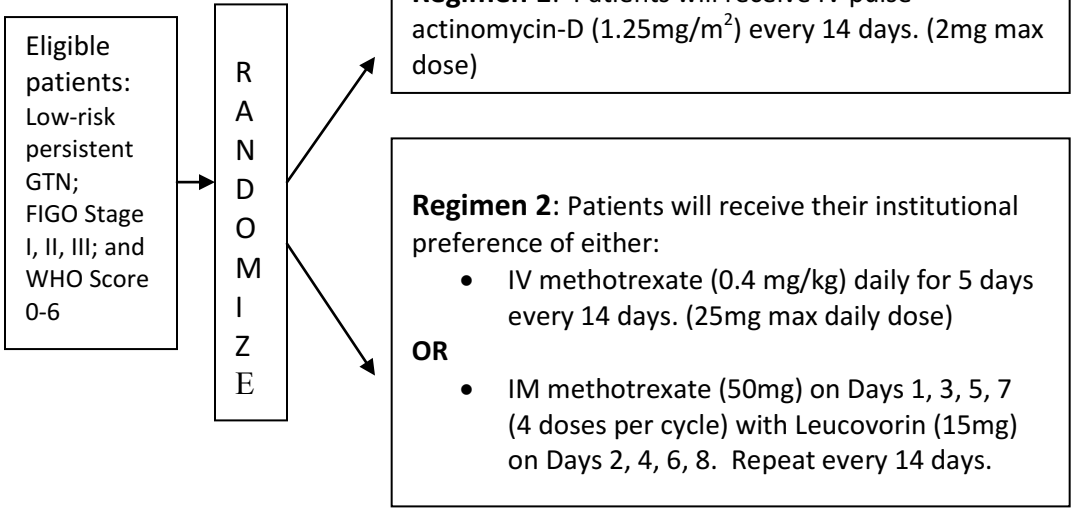
Includes Revisions #1-5

CONTACT INFORMATION		
To submit site registration documents:	**For patient enrollments:**	**Submit study**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSU REGULATORY@ctsu.coccg.org (for regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com	Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. GOG Statistical and Data Center at Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263 **Call GOG User support 716-845-7767 to obtain user name and password to submit electronic data** Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS. Note: Non-lead group institutions will order the following supplies from the CTSU Operations Office: hard copy GOG-0275 QOL scantron forms.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

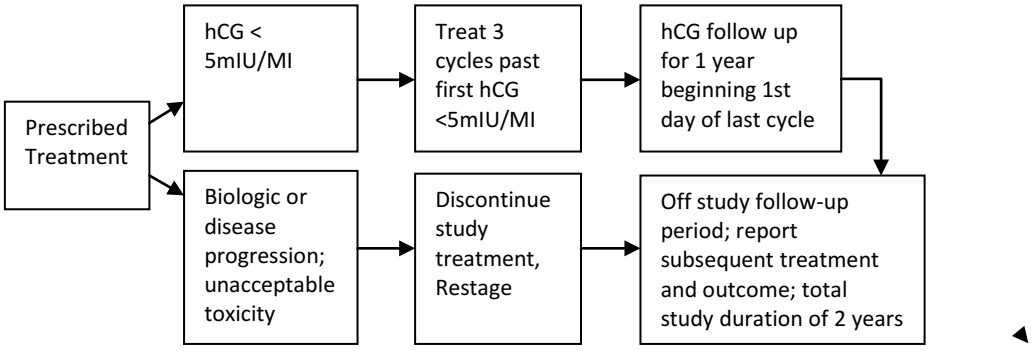
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy
The CTSU Web site is located at https://www.ctsu.org

OPEN TO PATIENT ENTRY JUNE 18, 2012
REVISED MARCH 11, 2013
REVISED MAY 28, 2013
REVISED NOVEMBER 24, 2014
REVISED

SCHEMA



Patients will be treated for **three cycles after hCG <5mIU/ml** or until evidence of biologic or disease progression or unacceptable toxicity despite dose modifications. Upon normalization of hCG (<5mIU/ml), hCG levels will then be monitored every 4 weeks for 52 weeks beginning with the 1st day of the last chemotherapy cycle.



Quality of Life surveys are to be obtained at 5 time-points:

- Prior to cycle 1
- Prior to cycle 3 (If off study therapy, 4 weeks after starting study treatment)
- Prior to cycle 5 (If off study therapy, 8 weeks after starting study treatment)
- Prior to cycle 7 (If off study therapy, 12 weeks after starting study treatment)
- 26 Weeks after starting study treatment

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1.0 OBJECTIVES

1.1 Primary Objectives

1.11 To test the hypothesis that treatment with multi-day methotrexate is inferior to treatment with pulse actinomycin-D in patients with low-risk gestational trophoblastic disease with respect to complete response.

1.2 Secondary Objectives

1.21 To describe the frequency of post protocol surgical treatment for each arm.

1.22 To describe the frequency of post protocol multi-agent chemotherapy treatment for each arm.

1.23 To compare multi-day methotrexate to actinomycin-D with respect to frequency and severity of adverse events in patients with low-risk gestational trophoblastic neoplasia.

1.24 To investigate the impact of treatment on overall QOL and explore the influence of treatment on issues such as body image, sexual functioning, and patient reported side effects and disruption.

1.25 To assess whether uterine artery pulsatility index (UAPI) can provide independent prognostic information predictive of single-drug resistance.

2.0 BACKGROUND AND RATIONALE

Prior Clinical Trial Evidence

Both methotrexate and actinomycin-D are effective first-line drugs for persistent low-risk gestational trophoblastic disease. There are several dosing/cycling options for each drug. When GOG-0174, a phase III randomized trial of bi-weekly IV actinomycin-D versus weekly IM methotrexate was initiated in 1999, the most commonly used North American regimen was low dose IM methotrexate.[1,15] In a follow-up phase II dosing study, the GOG demonstrated that escalating the methotrexate dose up to 50mg/m^2 did not significantly alter response when compared to the fixed dose of 30 mg/m^2 in the previous study.[16] Furthermore, Elit et al found that high dose methotrexate did not demonstrate significant additional benefit over the study dosage.[23] Single agent actinomycin-D was initially reported as a five-day parenteral regimen but it lost favor because of alopecia and nausea (Wong et al).[24] More recently single-injection actinomycin-D was reported to be as effective first treatment as weekly methotrexate.[19, 20, 22]

GOG-0174 demonstrated a higher complete response rate for bi-weekly actinomycin-D regimen than for the weekly IM methotrexate regimen.[1] GOG-0174 included patients with a World Health Organization (WHO) risk score of 0-6 and patients with metastatic

disease or choriocarcinoma. Of the 216 eligible patients, bi-weekly intravenous (IV) actinomycin-D at 1.25mg/m^2 was statistically superior to weekly intramuscular (IM) methotrexate at 30 mg/m^2 (complete response: 70 vs. 53%; p=0.01). Similarly, in patients with low risk GTN as defined prior to the 2002 WHO risk score revisions (risk score of 0-4 and excluding choriocarcinoma) response was 58 and 73% in the methotrexate and actinomycin-D arms, respectively (p=0.03). Both regimens were less effective if the WHO risk score was 5 or 6 or if the diagnosis was choriocarcinoma (complete response: 9 and 42%, respectively). There were two potential recurrences; one at four months (actinomycin-D) and one at 22 months (methotrexate). Not all patients completed follow-up. Both regimens were well tolerated.

While the results of GOG-0174 are compelling evidence that pulse actinomycin-D is the more effective single day regimen, many Trophoblastic Disease Centers continue to use multi-day methotrexate regimens because of a perception of higher complete response rates in the absence of a randomized controlled trial. Controversy exists over the relative toxicity and efficacy of these commonly used regimens compared with the pulse actinomycin-D regimen.

Rationale for Selected Approach and Trial Design

The abrupt psychological shift experienced by a woman facing a diagnosis of gestational trophoblastic disease can be traumatic.[4] The excitement and anticipation of a future child to the sadness associated with the loss of a viable pregnancy to the anxiety and fear connected with a potentially malignant and life-threatening condition is profound and certainly unique to this disease entity.[5] However, low-risk gestational trophoblastic neoplasia (GTN) is a highly curable disease.

There are many effective single-drug chemotherapy regimens; however, the choice of both the drug and regimen is highly institution specific. There is no consensus on the best regimen for the primary treatment of GTN. While the most important objective of treatment in these young reproductive-aged women is effectiveness and lower risk of exposure to multi-drug second-line regimen, other considerations, including short-term toxicity, side-effects and treatment issues (i.e., cost efficiency, administration, patient preference and compliance) and QOL become paramount and warrant investigation as targeted outcomes. The goal would be to identify the most effective single agent chemotherapy, recognizing the significant negative impact of multi-agent chemotherapy on possible reproductive issues (early menopause),[6] risk of secondary cancer[7, 8] and ultimately QOL if multi-agent chemotherapy is required for cure.

The GOG-0174 study conducted by members of this study team, as mentioned above, examined biweekly actinomycin-D and weekly methotrexate and both regimens were well tolerated.[1] However, questions remain regarding differences in drug dosages, schedules, administration methods and length of therapy delivered after hCG normalization.[9] These concerns have been addressed within the design of the proposed randomized clinical trial by clearly outlining the treatment modalities for each study arm. The proposed study will also include areas not formally assessed in previous studies

using patient reported outcomes (PROs) to prospectively examine patient's overall QOL during the treatment process and immediate surveillance period. This will enable us to examine to the influence of treatment factors, short-term toxicities, and side effects on QOL, which may be crucial when survival outcomes are both excellent and expected to be equivalent.

This comparative effectiveness research has the potential to establish a new resource sensitive standard acceptable worldwide. This study will compare pulse actinomycin-D with the standard therapies used at the expert centers around the world. If the complete response rate for multi-day methotrexate is not better than bi-weekly pulse actinomycin-D, women will have a clear option for a more convenient, less toxic treatment regimen. QOL assessment will also provide valuable information from the patient's perception to be included in determining a worldwide standard.

Upfront complete response is an important endpoint because approximately 25%[1, 2] of women failing to achieve complete response with their initial chemotherapy regimen ultimately require surgery and/or multi-agent etoposide based chemotherapy. In GOG-0174 the complete response rate for pulse actinomycin-D was 71%.[1] Lurain et al.[2] described the toxicity and efficacy of the 5 day methotrexate regimen noting 4.7% of patients experienced toxicity requiring a change from methotrexate to actinomycin-D and an 89.3% (226/253) complete remission rate to initial single-agent methotrexate (0.4mg/kg IV push qd x 5d qo week). Berkowitz described the New England Trophoblastic Disease Center experience with the 8 day methotrexate with folinic acid rescue regimen with a 90% complete response rate.[3] A recent Cochrane review concluded that the 8 day regimen did not offer an advantage in efficacy or adverse event profile over the 5 day regimen.

While past research has described various treatment outcomes from chemotherapy and surgery, the health consequences and psychosocial aspects have been minimally explored and rarely in a prospective manner or with PROs. Survey studies have shown quality of life to be negatively impacted by chemotherapy, regardless of the regimen.[10,11] A trend of lower QOL exists between those requiring chemotherapy treatments to those who do not.[10] In a cross-sectional survey study, women with active disease (n=11) demonstrated greater concerns, fear and threats to self-esteem than women in remission.[11] Yet, another recent study described no significant effect of chemotherapy on QOL, but the number of patients surveyed during active treatment (out of n=54) was not provided.[12] Formal assessment of QOL over the course of treatment will allow for a more thorough examination of possible treatment influences on QOL such as delivery, number of chemotherapy cycles, type of chemotherapy, compliance and life disruption.

Attention to acute side-effects/short-term toxicities and their impact on QOL is an important area for consideration and noted need in the comparison of chemotherapy regimens.[9] This is of particular relevance in a population with an excellent survival outcome of more than 98%.[8] For example, the side-effects of alopecia is often under-reported in oncology clinical trials,[1] and has been coded as a dermatologic event in past studies. Difficulty with body image (unattractive, feeling less of a woman) and sexuality

(difficulty with sex and fear that sex would worsen disease) have been described in women with active disease with greater levels of distress.[11] Patient reported outcomes are needed to understand patient's perception (i.e. body image) and the experience of treatment effects on QOL.

It is recognized that overall QOL is a multi-faceted domain including physical, functional, social, and emotional factors. We will examine these subcomponents within this study design based on the GTD/GTN literature. Our goal is to determine which treatment is best tolerated with less negative impact on QOL while simultaneously assessing the effectiveness of the proposed chemotherapies. Issues of social support, emotional well-being and gynecologic issues have been described as having influence on QOL in this population. For example, studies investigating QOL after GTD have identified greater social support ($p<.0001$) and less disease specific distress ($p<.0001$) to be associated with high quality of life scores.[5] In additional analyses, less gynecologic concerns (i.e., pain) were significant predictors of positive QOL.[5] Other research in women with a history of molar pregnancies found issues of emotional well-being (anxiety, depression)[10] and sexual dysfunction were experienced by participants.[10,13] While these studies highlight some significant psychosocial effects experienced by survivors of GTD, acute and short-term health consequences of newly diagnosed GTN patients requires further prospective investigation. In particular, psychosocial distress has been noted to be more pronounced in the initial months of diagnosis.[10]

This study will prospectively evaluate the effectiveness of two types of chemotherapy treatments and explore factors (social support/ emotional/ gynecologic issues) that may influence QOL. In addition, we will determine if these findings may vary by type of chemotherapy treatment, number, or length of treatment and/or in surveillance. Quality of life predictors of social support may also buffer distress in these women.[14] As we measure QOL within this study, we will also examine for potential buffering effects.

It should be noted that long-term toxicities have also been identified as an important area for future research. However, difficulties arise when studying this population, as many women are not followed at cancer centers beyond the 6 months after hCG normalization due to low recurrence rates.[1,8,9] Although it is recognized as important for further research, it is beyond the scope of this comparative effectiveness chemotherapy trial.

Rationale for Optional Doppler Ultrasonography of the Uterine Artery

Neo-angiogenesis, the formation of new blood vessels, is a critical step in tumorogenesis.[27] Neo-angiogenesis is associated with increased tumor growth, acquisition of metastatic potential, drug resistance and poor prognosis in a number of solid tumocenters such as breast, lung and ovarian cancer.[28,29,30,31] Histological asssessment of microvessel density (MVD) with CD34 immunostaining is used to assess angiogenesis in these tumors. In contrast, MVD assessment is not possible in GTN as biopsy is frequently contraindicated because of the risk of precipitating life-threatening hemorrhage in this highly vascular disease. Instead, the diagnosis is usually made on the basis of rising hCG levels post-molar pregnancy. Agarwal et al. previously proposed the

use of Doppler ultrasonography as a non-invasive alternative to assess tumor vascularity in GTN, using the uterine artery pulsatility index (UAPI).[32] The UAPI is inversely proportional to tumor vascularity, and a low UAPI is indicative of increased arteriovenous shunting, a feature of the abnormal neo-angiogeneisis characteristic of tumors. In that sudy of 164 patients with GTN, a UAPI of ≤1 was shown to be an independent predictor of methotrexate resistance (MTX-R) and in combination with the Charing Cross Hospital (CXH) scoring system improve prediction of MTX-R. In particular, the risk of MTX-R in patients with medium-risk CXH scores of 6–8 with a UAPI of ≤1 was increased to 72.7% from a baseline risk of 56.3% in this group. These findings suggested that UAPI might be a useful additional variable to incorporate into the prognostic scoring systems to help refine which patients might be treated with EMA-CO chemotherapy upfront.

To assess whether the UAPI could also contribute to the FIGO scoring system Agarwal et al. recently repeated this single center study. The results, published in 2012, confirm that UAPI is an independent predictor for MTX-R in low risk GTN patients (FIGO score 0-6) following a hydatidiform mole.[33] In this study, 239 patients were assessable for both UAPI and MTX-R. The median UAPI was lower (higher vascularity) in MTX-R compared with MTX-sensitive patients (0.8 vs 1.4, $p<0.0001$). In multivariate logistic regression, UAPI≤1 predicted MTX-R, independent of both CXH and FIGO scores. The risk of MTX-R in patients with a FIGO score of 6 and UAPI ≤ 1 was 100% vs 20% in patients with UAPI ≤ 1 (chi-sq. $p<0.0001$).

It was proposed that it might be helpful to consider adding the UAPI to the FIGO scoring system. We believe it would be helpful to first prospectively validate these findings in a multicenter study. This would demonstrate the utility of the approach across centers in many countries.

In the case of gestational trophoblastic tumors where nearly all patients are cured with existing therapies, the incorporation of UAPI into the scoring system would help to more accurately select patients for combination chemotherapy, resulting in less total treatment time and toxicity.[32] Based on these prior data, we are asking institutions to collect and report Doppler assessments of the uterine arteries, to further validate these findings in the context of a multi-center randomized prospective study, to determine if UAPI should be considered for incorporation in to FIGO scoring. While this is an optional study and does not preclude institutions from participating in the main study, we strongly encourage centers to participate, as the Doppler assessment can be conducted rapidly at the time of baseline staging ultrasound scans prior to commencement of chemotherapy.

2.1 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients who meet F.I.G.O. Stage I, II, or III criteria (See Appendix I-F.I.G.O. Staging Criteria) for low-risk gestational trophoblastic neoplasia (GTN): post molar GTN or choriocarcinoma (as defined below). Patients may have had a second curettage but must still meet GTN criteria below.

3.111 Post Molar GTN
For the purposes of this study, patients must have undergone evacuation of a complete or partial hydatidiform mole and then meet the criteria for GTN defined as:

3.1111 A < 10% decrease in the hCG level using as a reference the first value in the series of 4 values taken over a period of 3weeks (>50 mIU/ml minimum).
OR
3.1112 A > 20% sustained rise in the hCG taking as a reference the first value in the series of 3 values taken over a period of 2weeks (>50 mIU/ml minimum).
OR
3.1113 A persistently elevated hCG level a period of 6 months or more following the initial curettage (>50 mIU/ml minimum).

3.112 Choriocarcinoma

3.1121 Histologically proven non-metastatic choriocarcinoma.

OR
3.1122 Histologically proven metastatic choriocarcinoma if the metastatic site(s) is restricted to one (or more) of the following: vagina, parametrium, or lung.

3.12 W.H.O. risk score 0-6 (See Appendix II-W.H.O. Risk Scoring Criteria).

3.13 Patients must be willing to practice effective contraception for the duration of the study.

3.14 Patients must have normal hepatic, hematologic, and renal function:
WBC ≥ 3,000 cells/mcl;
Granulocytes ≥ 1500/mcl;
Platelets ≥ 100,000/mcl;
Creatinine ≤ 2.0 mg/dcl; Bilirubin ≤ 1.5x institutional normal;
ALT, AST and alkaline phosphatase ≤ 3x institutional normal.

3.15 Patients who have met the pre-entry requirements specified in Section 7.0.

3.16 Before enrolling a patient, the institution must verify the availability of an adequate supply of methotrexate for a full course of therapy.

3.17 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.18 Patients must be 18 years of age and older.

3.2 Ineligible Patients

3.21 Patients who do not have GTN as defined in Section 3.11.

3.22 Patients with non-gestational choriocarcinoma.

3.23 Patients who have previously been treated with cytotoxic chemotherapy. However, patients who received prior low-dose methotrexate for treatment of an ectopic pregnancy will be eligible for this study.

3.24 Patients who have received prior pelvic radiation.

3.25 Patients with placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT).

3.26 Patients with GOG Performance status of 3 or 4.

3.27 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.28 Patients whose circumstances at the time of study entry do not permit completion of the study or required follow-up.

3.29 Patients who wish to breast-feed during treatment.

4.0 STUDY MODALITIES

4.1 Actinomycin-D

4.11 Other Names: DACTINomycin, DACT, or ACT-D, Cosmegen®

4.12 Description: Injection of actinomycin-D is a lyophilized powder. In the dry form, the compound is an amorphous yellow to orange powder. Injection of actinomycin-D is supplied in vials containing 0.5mg (500 micrograms) of actinomycin-D and 20.0mg of mannitol.

4.13 How Supplied: Commercially available.

4.14 Storage and Stability: Protect from light. Store in a dry place between 20^0 to 25^0 C (68^0 to 77^0 F) (86°F). Cosmegen® (actinomycin-D for injection) has been found to maintain full activity for 24 hours, when stored both at room temperature or under refrigeration, if reconstituted as recommended.

4.15 Preparation: Reconstitute actinomycin-D by adding 1.1 mL of sterile water for injection (without preservative) using aseptic precautions. The resulting solution of actinomycin-D will contain approximately 500mcg or 0.5mg per ml. When reconstituted, the solution is clear and gold-colored.

4.16 Administration: 1.25 mg/m^2 (maximum dose 2mg) by slow IV push over 15 minutes or institution standard (via running IV of 0.9NS with brisk blood return every 1/2mL). Provide 75mL of 0.9NS flush prior to and after infusion. If evidence of extravasation occurs during administration, the infusion should be stopped immediately and completed via another vein, preferably in opposite arm. If extravasation is suspected, intermittent application of ice to the site for 15 minutes four times a day for 3 days is recommended. **(03/11/2013)**

4.17 Adverse Effects: Consult the package insert for the most current and complete information.

4.2 Methotrexate

4.21 Other Names: MTX, amethopterin

4.22 Description: Methotrexate is a folate antimetabolite.

4.23 How Supplied: Commercially available. Injectable methotrexate is currently available in 25mg/mL injection in a 10mL vial. **(03/11/2013)**

4.24 Storage and Stability: The drug will only be safe to use within 24 hours at room temperature.

4.25 Preparation:
For IM administration, the methotrexate 25mg/mL is drawn up in a syringe with diluent. If necessary for patient comfort, the dose may be divided into two syringes.

For IV administration, the methotrexate is prepared in a syringe with diluent of normal saline for a total volume of 5cc.

4.26 Administration: **(11/24/2014)**
Intramuscular Administration: Inject 50mg methotrexate deeply into the upper outer quadrant of the buttock or institution standard. Aspirate prior to injection to avoid injection into a blood vessel.
Intravenous administration: 0.4mg/kg methotrexate (maximum daily dose of 25mg) injected as a slow push via free-flowing IV infusion or via 25g butterfly needle with 3cc 0.9NS flush prior to and post administration of the drug with brisk blood return every 1cc or institution standard.

4.27 Adverse Effects: Consult the package insert for the most current and complete information.

4.3 Leucovorin

4.31 Other Names: Calcium folinate, folinic acid, citrovorum factor, 5-formyl tetrahydrofolate

4.32 Description: Leucovorin is a reduced folic acid. Leucovorin is used in combination with other chemotherapy drugs to either enhance effectiveness, or as a "chemoprotectant".

4.33 How Supplied: Commercially available. Tablet for oral administration in 5 and 10 mg scored white tablets and also in 15 and 25mg scored yellow tablets.

4.34 Storage: Store away from light, excess heat and moisture and at room temperature of 15°C to 30°C (59°F to 86°F).

4.35 Administration: This study will use oral administration of Leucovorin. Patients receiving IM methotrexate will be instructed to take Leucovorin PO between 24 -30 hours after the preceding injection. If a patient misses a dose of Leucovorin she should be instructed to take the pill as soon as she remembers it unless it is within 12 hours of the next scheduled methotrexate injection. If it is 12 hours or closer to the next IM methotrexate injection, the patient should be instructed to skip that dose.

4.36 Adverse Effects: Allergic reaction: rash, itching, facial flushing (rarely severe); Nausea and vomiting are rare. Please consult the package insert for additional information

4.4 Pathology Requirements

4.41 Eligibility Criteria: Patients with histologically proven stage Stage I, II or III gestational trophoblastic disease (hydatidiform mole or choriocarcinoma) are eligible. Patients with non-gestational choriocarcinoma, placental site trophoblastic tumor (PSTT) or epithelioid trophoblastic tumor (ETT) are not eligible.

4.42 Requirements: Review of slides will be performed by the pathology committee at the semi-annual GOG business meetings. Slides must be submitted to document the initial diagnosis of partial mole, complete hydatidiform mole, or choriocarcinoma. If invasive or metastatic gestational trophoblastic disease is documented histologically, slides from those specimens must also be submitted for pathology committee review. Registration specimens will be classified histologically as either choriocarcinoma, partial mole or complete mole, if possible. See Sections 7.2 and 10.2 for additional instructions and requirements.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

5.1 Registration Procedures **(11/24/2014)**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

5.11 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

5.12 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

5.121 IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

5.122 Downloading Site Registration Documents:

Site registration forms may be downloaded from the GOG-0275 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
Click on the Protocols tab in the upper left of your screen
Click on the *NCTN NRG* link to expand, then select trial protocol # 0275
Click on the Site Registration Documents link

5.123 Requirements For GOG-0275 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
- CTSU RT Facilities Inventory Form
  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in IROC Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

5.124 Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

5.125 Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
Click on the Regulatory tab at the top of your screen
Click on the Site Registration tab
Enter your 5-character CTEP Institution Code and click on Go

5.2 Patient Entry and Registration **(11/24/2014)**

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the GOG web menu page by clicking on the OPEN link.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

  Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

  Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

NOTE: Each participating site must make a ONE TIME declaration of the methotrexate administration schedule to be used exclusively at their site. Prior to the registration of a site's first patient, a representative must sign on to the GOG Web Menu and use the GOG methotrexate declaration application located under the Registration column. Sites will indicate the methotrexate administration schedule that will be used exclusively at the site for the duration of the study. The representative will choose the methotrexate schedule from a drop down list provided. The site representative must be in the GOG roster with an active status at the site who is a DM1, DM2, PI1, or PI2. The site must have approved IRB status to make the declaration. Once a site registers their first patient, they will no longer be able to change the selected methotrexate administration schedule. This schedule must be used for all other patients put on this study. (03/11/2013)

The methotrexate administration choices are as follows:

IV methotrexate daily for 5 days.

OR

IM methotrexate on days 1,3,5,7.

5.3 Treatment Plan

One of two treatment regimens will be randomly allocated in equal proportions within strata. The strata are determined by the following factors:

- Country where treatment is given (US, Canada, Japan, Korea, Australia, United Kingdom, etc.)
- Multi-day methotrexate regimen (8- or 5-day) used by the participating site as stated on the one time methotrexate declaration form.

5.31 Study Regimens

Eligible, consented patients will be randomized to one of the following two study regimens:

Regimen 1: Patients will receive IV pulse actinomycin-D (1.25 mg/m^2) once every 14 days. Maximum dose is 2 mg.

Regimen 2: Patients will receive their institutional preference of either IV methotrexate (0.4mg/kg) daily for 5 days every 14 days with a maximum daily dose of 25 mg.
OR
IM methotrexate (50mg) on Days 1,3,5,7 (4 doses per cycle) with Leucovorin (15mg) orally on Days 2, 4, 6, 8 within 24-30 hours of the preceding day's injection. Repeated every 14 days.

Leucovorin Administration

Patients receiving IM methotrexate will be instructed to take Leucovorin PO between 24 -30 hours after the preceding injection. If a patient misses a dose of Leucovorin she should be instructed to take the pill as soon as she remembers unless it is within 12 hours of the next scheduled methotrexate dose. If it is 12 hours or closer to the next IM methotrexate injection, the patient should be instructed to skip that dose.

A medication calendar (Appendix IV) is provided for patients to record intake of Leucovorin. Completed calendars should be returned with empty bottles of drug. **(03/11/2013)**

5.32 Potential Drug Interactions

It is anticipated that nausea and vomiting may be a side effect of both methotrexate and actinomycin-D. Institutional guidelines for antiemetic administration should be followed. It is suggested that NCCN guidelines be followed (see GOG-0275 webpage to download). **(03/11/2013)**

Supplements with a high folic acid level should not be taken while on study.

In addition, patients should be advised to avoid taking NSAIDS while on treatment with methotrexate and to discuss with their physician.

Use of sunscreen should be advised for all study patients as actinomycin-D and methotrexate can cause skin reactions when exposed to sun.

5.33 Treatment Schedule

A Cycle is 14 days. The patient must receive her first cycle of treatment within 2 weeks of entry onto the study.

A call (by site staff) will be placed to the patient prior to every other treatment cycle to (1) assess toxicity and (2) encourage compliance.

Patients will be treated for three cycles after hCG<5mIU/ml or until evidence of treatment failure (biologic progression), disease progression or unacceptable toxicity despite dose modifications. Upon normalization of hCG (<5mIU/ml), patients will be treated with three additional cycles. HCG levels will then be monitored every 4 weeks beginning with the 1st day of the last chemotherapy cycle, for the next 52 weeks to complete one full year of follow up. QOL questionnaires are to be completed by all patients at 26 weeks.

Patients will be treated for a maximum of 20 cycles if hCG remains elevated (above 5mIU/ml). **(05/28/2013)**

5.34 Doppler Ultrasound to Measure UAPI

At the time of the baseline pelvic ultrasound, centers participating in the optional UAPI component of the study should use Doppler ultrasound to measure the left and right uterine artery pulsatility indices (UAPI). UAPI can be calculated automatically by most machines using the autotrace functionality. The PI value is calculated by the machine and appears on the report.

A representative sample of 3 cardiac cycles (pulses) should be measured for the left artery as close to the uterus as possible. Perform this

measurement three separate times and record the lowest of the three PI values on the Pelvic Ultrasound GTN (PUG) form. Repeat this same process for the right uterine artery, recording the lowest PI value on the PUG.

If Doppler ultrasonography is performed but the UAPI is not recorded, please mark "not specified" on the report. If your site does not have access to Doppler ultrasonography, please record "not done" on the Pelvic Ultrasound Measurements Report.

5.4 Criteria for Removal from Treatment

5.41 Inability to tolerate the lowest dose because of toxicity (e.g., inability to tolerate the allocated treatment due to repeated grade 4 toxicity that does not respond to supportive measures).

5.42 Treatment failure (biologic progression) or disease progression that is defined in Section 8.

5.43 Treatment non-compliance that is defined to be less than 75% of planned or protocol-modified dose over 3 cycles.

5.44 Patients may refuse further intervention or completely withdraw consent from the study at any time for any reason. If a patient elects to discontinue further study treatment and/or intervention prior to protocol specification and elects to receive alternate therapy, this information should be specifically documented as consent allows. Additionally, if the patient withdraws from the treatment portion of the study, hCG levels should still be obtained per protocol schedule.

5.45 Pregnancy

5.5 Quality of Life Assessment

Quality of Life surveys are to be obtained at 5 time points:

- Prior to cycle 1
- Prior to cycle 3 (If off study therapy, 4 weeks after starting study treatment)
- Prior to cycle 5 (If off study therapy, 8 weeks after starting study treatment)
- Prior to cycle 7 (If off study therapy, 12 weeks after starting study treatment)
- 26 weeks after starting study treatment

See Section 8.5 for complete overview of QOL study survey.

6.0 TREATMENT MODIFICATIONS

6.1 Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation above the starting dose will be employed for either drug.

6.2 The maximum permitted dose of actinomycin–D will be 2 mg per cycle. The maximum permitted dose of daily IV methotrexate will be 25mg per day. **(03/11/2013)**

6.3 Dose Modifications **(05/28/2013)**

Study Drug	**2 Level reduction**	**1 Level reduction**	**Initial dose level**
Actinomycin-D	0.75mg/m^2	1.0mg/m^2	1.25mg/m^2
Actinomycin-D for patients who are receiving the maximum dose (2mg) due to BSA	1.28mg	1.6mg	2.0mg
IV Methotrexate (0.4mg /kg)	3 days only	4 days only	Daily for 5 days
IM Methotrexate (50mg) Leucovorin (15mg)	Discontinue study treatment	Increase Leucovorin dose to 30mg.	50mg

6.4 Hematologic Toxicities

6.41 Myelosuppression as demonstrated by pretreatment counts:

6.411 Treatment will be delayed for 1week if the following parameters are not met on the day 1 of each cycle:

Granulocytes ≥ 1500 cells/mcl and platelets ≥ 100,000/mcl

If any course is delayed more than two weeks from the scheduled administration date, the dose of the start of the next cycle will be decreased by one dose level.

6.412 In the event that a patient experiences Grade 4 myelosuppression, G-CSF may be used at the discretion of the investigator. However, its use, including the duration and timing of administration and dosage, must be documented on Form D2R.

6.5 Gastrointestinal and Other Toxicities

6.51 Nausea and emesis:

6.511 Nausea and emesis are anticipated with all regimens but are not expected to be incapacitating. Reassessment of IV and oral antiemetics for appropriate adjustments should be considered. Please refer to the NCCN guidelines (on the GOG-0275 webpage) for supportive care guidelines. **(03/11/2013)**

6.512 No dose adjustment is to be made for nausea and emesis.

6.513 Treatment will be delayed for Grade 3 toxicity until resolution to Grade 2 or less is reached. Protocol treatment will be discontinued for Grade 4 toxicity.

6.52 Stomatitis and other GI, renal or hepatic toxicities:

6.521 If a patient experiences Grade 2 stomatitis, treatment will be delayed until resolution to Grade 1. Grade 3 stomatitis will require a one dose level reduction at the start of the next cycle once resolution to Grade 1 is reached. Protocol treatment will be discontinued for Grade 4 stomatitis.

6.522 Treatment will be delayed for Grade 3 gastrointestinal, renal or hepatic toxicity until resolution to Grade 2 or less is reached. Protocol treatment will be discontinued for Grade 4 toxicity

6.53 Pleuritis:

6.531 For Grade 3 pleuritis, hold treatment until resolution to Grade 2 or lower.

6.532 For Grade 4 toxicity the patient will be taken off study treatment.

6.54 Potential modifications for other non-hematologic toxicities not listed, with an impact on organ function of Grade 3 (or greater) require discussion with one of the study chairs.

Applicable to all toxicities, study treatment should be discontinued if treatment is delayed longer than 2 weeks.

7.0 STUDY PARAMETERS

7.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s):

Parameter	Prior to Study Entry	Prior to Each Cycle	Prior to Every Other Cycle	Following Completion of Treatment Weeks 1-26 (Months 1-6) (03/11/2013)	Following Completion of Treatment Beginning Week 27 (Month 7) (03/11/2013)	At Diagnosis of Disease Progression or Treatment Failure (biologic progression) and Follow-up (03/11/2013)
History & Physical, including concomitant medication tracking	1	X		2		X
Pelvic Exam	1					
CBC/Differential/Platelets	3	X				X
hCG Test	3	X		4	4	X
Serum chemistry (total bilirubin, creatinine, alkaline phosphate, SGOT(AST), SGPT(ALT), sodium, potassium, albumin, glucose, BUN)	3	9				X
LDH	10					
Toxicity Assessment	1	X, 7				X
Calculate WHO Score	1					X
FIGO Staging	1					X
Pelvic Ultrasound	1,11					X
CXR for WHO Scoring	1					X
CT or MRI of the brain, if abnormal CXR or if clinically indicated	1					X

Follow-up phone call by site staff			X	6	6	
QOL Assessments (FACT-G and FACIT)	3	5		5		5
Report subsequent treatment and outcome				12 **(03/11/2013)**	12 **(03/11/2013)**	8

1. Must be obtained with 28 days prior to initiating protocol therapy. If the pelvic exam is abnormal, it should be repeated as needed.
2. For patients who have responded to treatment; must be obtained at 3 months and 6 months after completing treatment (week 12 and week 24) (+/- 7 days). **(03/11/2013)**
3. Must be obtained with 14 days prior to initiating protocol therapy.
4. For patients who have responded to treatment; must be obtained every 4 weeks (or monthly +/- 3 days) for 1 year after completing treatment. **(03/11/2013)**
5. Prior to cycle 1, 3, 5, 7 and at 26 weeks (refer to section 7.42 if pt off chemotherapy treatment)
6. Call will be made if pt misses treatment or follow-up visit.
7. 2-4 weeks after last cycle of study treatment.
8. For patients discontinuing treatment due to treatment failure (biologic progression), disease progression, or unacceptable toxicity, report disease status, survival status and pregnancy status/outcome quarterly via the Q form for a period ending 2 years after study entry. **(03/11/2013)**
9. Prior to cycle 1, 3, 5, and 7.
10. Must be obtained within 14 days prior to study entry and if abnormal, repeat prior to each cycle.
11. Doppler ultrasonography (optional sub-study) of both the left and right uterine arteries should be performed at the time of the pelvic ultrasound, to determine the uterine artery pulsatility index (UAPI). This is automatically calculated and should be included in the ultrasound report (see section 5.24).
12. For patients who have responded to treatment, report disease status, survival status and pregnancy status/outcome quarterly via the Q form for a period ending 2 years after study entry. **(03/11/2013)**

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Eligibility:

H&E stained glass slides to document the following: 1) the initial diagnosis of gestational trophoblastic disease (all patients) and 2) any invasive or metastatic tumor that is histologically proven.

When submitting pathology material to the GOG SDC, individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label with collection date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report. Ship pathology slides, two copies of both the Pathology Form F and the official pathology report directly to the Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting pathology reports and Form F. Please see sections 4.4 and 10.2 for additional requirements.

7.3 Translational Research

Not Applicable

7.4 Quality of Life

7.41 Refer to sections 5.4; 7.1; 7.42; 8.6 and 10.2 for description and collection times of the QOL study assessments.

7.42 Timing of the Quality of Life Assessments

To measure the difference in QOL following initiation of treatment on this study, the following time points for QOL assessments are planned:

7.421 At baseline (prior to cycle 1)
7.422 Prior to cycle 3 (4 weeks after starting study treatment if off study treatment prior to cycle 3)
7.423 Prior to cycle 5 (8 weeks after starting study treatment if off study treatment prior to cycle 5)
7.424 Prior to cycle 7 (12 weeks after starting study treatment if off study treatment prior to cycle 7)
7.425 26 weeks after the start of study treatment.

While still on study treatment, assessments will be completed as planned at initial treatment visits for appropriate cycles prior to obtaining knowledge of hCG value changes or treatment changes.

7.43 Quality of life forms will be provided by the SDC upon request. Requests for non-English versions should be made to the Statistical and Data Center.

7.44 Whenever possible, the QOL survey should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed, and before test results are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.45 The Quality of Life Liaison (GOG Nurse/Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.46 The GOG Nurse/Data Manager should read the instructions printed on the questionnaire to the patient and ensure that the patient understands the instructions. It is important to assure the patient that all material on the

questionnaire is confidential and will not be shared with the health care team, and that it will not become part of the medical record.

7.47 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.48 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's response.

7.49 Review the questionnaire for completeness before the patient leaves.

7.491 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.492 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.410 It is essential that the questionnaires be completed according to the schedule described in Section 7.42.

7.411 If the patient refuses or cannot complete the questionnaire at any time, she should be asked to do so at the next scheduled administration time.

7.412 Prior to submitting the QOL Scantron to the GOG Statistical and Data Center, be sure the following information is recorded and coded in:

a) patient's complete GOG number
b) date of form completion
c) study time point for which the form is being completed

8.0 EVALUATION CRITERIA

8.1 Evaluability

8.11 Patients evaluable for response are those who have received one or more cycles of drug and have a sufficient number of bi-weekly test results to fulfill one of the response categories.

8.12 Patients are evaluable for assessment of adverse effects (toxicity) if they have received a minimum of one injection or infusion of treatment.

8.2. Clinically Assessed Response

Institutional hCG test results will be used to define the dichotomous primary clinical response measure and to evaluate the primary objective. Reporting should be in terms of the best response achieved in a given case.

8.21 Complete Response will be defined as 3 consecutive bi-weekly values of hCG<5 over a minimum of 4 weeks of normal hCG values with no values greater than 5 mIU/ml on the BMR form. Report best response as "Complete Response" on Form Q0 per Section 10.2

8.22 Treatment Failure (biologic progression) is defined as:

8.221 A < 10% decrease in the hCG levels using as a reference first value in the series of 4 values taken over at least a 3-week period.
OR

8.222 A > 20% sustained rise in the hCG taking as a reference the first value in the series of 3 values taken over at least a 2-week period.
OR

8.223 Two consecutive hCG levels above 5 mIU/ml after the institutional normal has been reached taken at least one week apart.
OR

8.224 hCG levels remain elevated above 5 mIU/ml after 20 cycles of treatment. **(05/28/2013)**
OR

8.225 New metastatic disease based on either clinical findings or radiologic Investigations while on study treatment or during the follow-up period.

If any of the criteria in 8.221-8.225 are met then report "Biologic Progression" as best response on Form Q0.

8.23 Persistent disease is defined as 4 consecutive hCG values over 6 weeks that fluctuate within the range of 5 to 50 mIU/ml. Special consideration is required for patients with persistent hCG levels as this may not reflect treatment failure. For patients that develop persistent disease with less than 50 IU/ml, steps need to be taken to rule out false positive hCG, quiescent hCG, or phantom hCG. You should contact the study chair for discussion.

8.3 Disease Progression is defined as new metastatic disease findings from clinical or radiological investigations or a sustained elevation in hCG levels above 5 mIU/ml after documentation of a complete response (two consecutive levels above 5mIU/ml taken at least one week apart).

8.4 Other Objective Parameters

8.41 A cycle is defined as planned treatment for a period of 14 days.

8.42 The major toxicities of each regimen will be collected and compared using standard CTCAE version 4.0 toxicity criteria.

8.5 Quality of Life Assessments

The measures selected to comprise the Quality of Life assessment will include: 1) an overall quality of life measure addressing: physical symptoms, functional well-being, social well-being and emotional well-being, 2) supplemental items drawn from the FACIT scales addressing additional domains based on the GTN literature regarding potential toxicities, side-effects and treatment issues that can impact QOL and 3) two exploratory items about treatment factors. The QOL assessment will be administered at medical appointments and take approximately 15 to 20 minutes.

8.51 The Functional Assessment of Cancer Therapy (FACT-G) will be used to measure overall quality of life. The FACT-G is a 27-item scale measuring QOL in patients with cancer.25 It includes four subscales: 1) physical well-being {FACT-PW subscale} with 7 items (a=.82) - e.g., I have lack of energy; 2) functional well-being {FACT-FW subscale} with 7 items (a=.80), - e.g., I am able to work; 3) social well-being {FACT-SW subscale} with 7 items (a=.69) - e.g., I feel close to my friends; and 4) emotional well-being {FACT-EW subscale} with 6 items (a=.74) - e.g., I feel sad. The total alpha coefficient is.89, supported by factor analysis. Participants rate on a 5-point Likert-type scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). The subscales are summed for a total score ranging from 0-108, and a higher score indicates better QOL. The mean in a population of mixed cancer patients was 82.06 +/- 15.86. The FACT-G is available in multiple languages.

8.52 FACIT Supplemental Items: have been added to the QOL assessment based on a review of previous GTD/ GTN studies and identified toxicities and side effects from actinomycin-D and methotrexate noted in the literature. As the FACIT items are available in multiple languages, specific items were selected from the FACT disease specific subscales addressing potential factors that may influence the QOL of GTN patients undergoing chemotherapy treatment. Three items from FACT-N (Neutropenia) addressing blood counts, energy and mouth sores; Three items from the FACT-O (ovarian) addressing hair loss, appearance; Three items from FACT-Cx (cervical) addressing body image & sexual function and two from FACT-En (endometrial) addressing fatigue and gyn concern (pain). These items are also available in multiple languages.

8.53 Two exploratory items were created specific to treatment concerns: 1) Likert scale evaluation degree of life disruption from chemotherapy treatment and 2) rank item addressing factors associated with chemotherapy treatment (e.g. requirement per week and length of time per treatment). These will be available for an exploratory analysis in English speaking patients.

9.0 DURATION OF STUDY

Patients will be treated for three cycles after hCG <5mIU/ml or treatment failure (biologic progression), disease progression or unacceptable toxicity despite dose modifications. All subjects will be followed for a period ending 2 years after study entry. Quality of life will be assessed for all study patients at 26 weeks from the start of treatment, regardless of treatment status.

NOTE: The Q0 form is due at treatment completion (See Section 10.2). The Q form is due quarterly during the follow-up period. HCG values will be reported every 4 weeks on the BMR form.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT **(11/24/2014)**

10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational or commercial agents, and role of the pharmaceutical sponsor, an AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP-AERS. Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	7 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:
CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although aCTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

- There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.2 GOG DATA MANAGEMENT FORMS

The following GOG forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. GOG Protocol forms and instructions can be submitted through or printed from the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. Pathology material (Form F, pathology reports and slides) should be submitted together via mail. The GOG Uploader Application in SEDES is an alternate method for submitting Form BDR, operative reports, Form F and pathology reports to the GOG SDC.

Form[Δ]	**Due within**		**Copies***	**Comments**
	Weeks	**Event**		
Form R (Registration Form) Form SCT - entry (WHO Scoring Form for GTT)	2 2	Registration Registration	N/A N/A	Mandatory Submission via SEDES
Form OST (Trophoblastic On Study Form) Form PUG (Pelvic Ultrasound GTN Form)	2 2	Registration Registration	N/A	Mandatory Submission via SEDES
Ultrasound Report Chest X-ray Report Brain MRI or CT Report, if lung mets or clinically indicated	4 4 4	Registration Registration Registration	1 1 1	Submit via postal mail or upload online via SEDES labeled with patient identifier
Operative report – initial curettage Operative report – second curettage, if applicable	6 6	Registration Registration	1 1	Submit via postal mail or upload online via SEDES labeled with patient identifier
Pathology Material Initial curettage (all patients) and invasive/metastatic tumor (if histologically documented): Form F (Pathology Form) Pathology Report Slides	 6 6 6	 Registration Registration Registration	 2 2 **	 Submit together to SDC via postal mail or upload online via SEDES**
Form BMR (Biomarker Reporting Form) report required hCG values during treatment	2	Every 4 weeks	N/A	Mandatory Submission via SEDES
Form BMR (Biomarker Reporting Form) report required hCG values during follow-up period	2	Every 4 weeks	N/A	Mandatory Submission via SEDES
QOL Scantron Form*** Scantron Form prior to cycle 1 Scantron Form prior to cycle 3 Scantron Form prior to cycle 5 Scantron Form prior to cycle 7 Scantron Form for week 26	 2 6 10 14 28	 Treatment start Treatment start Treatment start Treatment start Treatment start	 1 1 1 1 1	 Submit the original Scantron form to the GOG SDC via postal mail

Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	N/A	Mandatory Submission via SEDES
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle	N/A	Mandatory Submission via SEDES
Form SCT – treatment failure (WHO Scoring form for GTT)	4	Completion of study treatment	N/A	Mandatory Submission via SEDES
Ultrasound Report Chest X-ray Report	4 4	Treatment Failure Treatment Failure	1 1	Submit via postal mail or upload online via SEDES labeled with patient identifier
Form Q0 (Treatment Completion Form)	2	Completion of study treatment	N/A	Mandatory Submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression, death, normal follow-up	N/A	Quarterly for 2years

* The number of required copies including the original form that must be sent to the Statistical and Data Center.

** At least one representative H&E stained slide (or slides) documenting the initial diagnosis of gestational trophoblastic disease and any invasive or metastatic tumor that is histologically proven. Please see sections 4.4 and 7.2 for additional requirements and instructions.

*** Quality of life Scantron forms may be ordered online via the GOG website under GOG Web Menu/Tools/Order forms.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly by the January 31, April 30, July 31 and October 31 due dates to CTEP by electronic means.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design and Treatment Randomization:

This study is designed as a two arm randomized phase III non-inferiority trial with a control arm using actinomycin-D (ACT-D) and an experimental arm using one of two multi-day methotrexate (MTX) regimen chosen by the participating site. The design will provide a direct assessment of the null hypothesis that the efficacy attributed to multi-day methotrexate regimens is inferior to that of ACT - D given every two weeks. Each IRB-approved participating site will declare upfront which MTX regimen they will use for the duration of the trial.

Prior to patient registration, eligibility will be reviewed by FFS verification. The sequence of treatment assignments will be concealed from institutions and patients until registration with verification of eligibility. Patients will be registered by the participating site through OPEN and randomization will be carried out centrally by the GOG Statistical and Data Center. The randomization will be stratified by the country (a surrogate for health care system) where treatment is given and the multi-day methotrexate regimen to be used by the institution using a minimization procedure that tends to allocate two study arms in a ratio of 1 to 1 within strata.

11.2 Efficacy and toxicity measures

The principal observations for evaluating the therapeutic efficacy and safety of treatments are listed below (see Section 8 for definitions).

11.21 Primary efficacy endpoint: complete response vs, treatment failure

11.22 Safety endpoints: severity of adverse events

11.23 Factors to be tested for association with treatment failure: W.H.O. risk score, choriocarcinoma histology, uterine artery pulsatility index

11.3 Statistical study design and planned analyses of therapeutic efficacy

11.31 Accrual goal: 384 patients

The maximum target accrual includes an expected 5% of patients to be deemed ineligible after central review.

11.32 Accrual rate: Originally, 80 patients per year was the expected accrual rate. However during the first 3 years the accrual was much lower than anticipated. Efforts to expand accrual to international sites were completed near the end of the third year of accrual.

The following is a revised estimate of annual accrual rates over time.
Year 1: 9 Year 2: 14 Year 3: 27 Year 4+: ≥ 60

GOG accrual for protocol 174 averaged 31 patients per year. We expected increased GOG site participation based on the flexibility in the experimental arm. Assuming a 25% increase in accrual rate (40) from that observed on GOG 174 from GOG sites and additional accrual of 40 patients per year from non-GOG sites that have expressed support for this study the expected annual accrual rate was 80 patients. This accrual rate has been revised based on actual accrual through the first 2.5 years. **( )**

11.33 Study duration: 60 months assuming an average annual accrual rate of 80. Assuming the revised accrual rates, the accrual duration is expected to be 8.6 years or less. A follow-up period of up to 6 months may be necessary to observe and report response in all patients. Additional time may be necessary to obtain all required QOL assessments. All required follow-up will end 24 months following the last enrollment. **( )**

11.34 Primary hypothesis
The primary null hypothesis to be tested is that the complete response attributed to multi-day methotrexate treatment is inferior to that of actinomycin-D.

$$H_0: p_d - p_m \geq M_1 \text{ vs. } H_1: p_d - p_m < M_1$$

In this statistical representation of the primary hypothesis, p_d represents the proportion of complete responses on ACT-D, p_m represents the proportion of complete responses on multi-day methotrexate, and M_1 represents the non-inferiority margin.

11.341 Non-inferiority margin and effect of the active control: $M_1 = 0.05$ and $p_d = 0.70$

GOG 174, a randomized phase III clinical trial comparing weekly methotrexate to ACT-D, demonstrated a superior complete response rate to ACT-D over weekly methotrexate. Hence, ACT-D is considered the active control in this non-inferiority study. The estimated difference in response rates was 0.15. The response rate to ACT-D was 0.70. The non-inferiority margin for this study is defined to be 0.05, 1/3 of the effect of ACT-D relative to weekly MTX.

11.342 Type I error for non-inferiority: 0.05

11.343 Type I error for superiority: 0.05

11.344 Statistical power: 0.95 calculated under the alternative that $p_d = 0.70$ and $p_m = 0.80$

11.35 Primary analysis

This study design requires the assumption of a consistent effect size relative to ACT-D for both MTX regimens. The statistical analysis plan will incorporate a stratified primary analysis comparing the binomial proportion of complete responses between the treatment arms among eligible patients. A test of the difference in proportions responding will utilize a test statistic that does not pool the variance across treatment groups. In the event that the null hypothesis of inferiority is rejected, a test of the superiority of the methotrexate regimen will be carried out and reported. There will be approximately 80% power to detect an increase in response rate of 11% if the true response rate in the reference arm is 70%. Reports and publications will include a complete accounting of all patients registered to this study.

Statistical test characteristics: probabilities of accepting each regimen under different settings

Methotrexate response p_m	ACT-D response P_d	$p_d - p_m$	P(accept MTX| p_m, p_d)	P(accept ACT-D| p_m, p_d)
0.80	0.70	-0.10	0.95	0.05
0.70	0.70	0.00	0.27	0.73
0.65	0.70	0.05	0.05	0.95

Interim and final analysis plan details

Look #	Info Fraction	Sample Size	Error Spent Alpha	Error Spent Beta	Boundaries H0+	Boundaries H1+	Boundary Crossing Probabilities H0+	Boundary Crossing Probabilities H1+
1	0.55	201	0.0082	0.0082	-2.399	0.071	0.536	0.536
2	1.00	365	0.0500	0.0500	-1.670	-1.670	0.464	0.464

Under the null and alternative hypotheses, the average sample size is 277.

11.351 Delta value to reject H_0 at final analysis: $p_d - p_m < -0.0252$

In this case, the observed response rate to methotrexate will need to be at least 2.52% better than that of actinomycin-D at the final analysis to accept methotrexate with its associated intensive scheduling.

11.352 Compliance monitoring:

Compliance to protocol treatment will be monitored for early discontinuation or non-protocol based dose adjustments. The total dose reported will be compared to the planned or protocol modified dose for each cycle.

11.353 Exploratory analysis of treatment efficacy:

An indirect comparison of the Multi-day regimens can be performed by assessing the relative effects across stratum of each methotrexate regimen against the control arm. This would be

considered an exploratory analysis and used to provide an approximate evaluation of the assumption of a constant effect size across multi-day regimens.

11.36 Interim analysis

An interim analysis plan is outlined above assuming the interim analysis occurs at exactly 55% of the information fraction. The information fraction is estimated by the number of eligible patients evaluated for response at a given time divided by the target sample size of eligible patients. However, the timing of the interim analyses will likely vary from this exact schedule for practical reasons. At the interim analysis, the test statistic for the primary analysis will be compared with the critical boundaries defined by the statistical design parameters described above an O'Brien and Fleming alpha spending function as proposed by Lan and DeMets. If a boundary is crossed, consideration will be given to terminating study accrual, if still active, and/or early release of data. Additional decisions may include recommendations on instructions for patients on study treatment. These rules are non-binding.

The results of interim analyses are scheduled to be reviewed by the GOG Data Safety and Monitoring Board (DSMB) at its semi-annual meetings. This committee meets in January and July each year. The precise dates for these meetings are set more than one year in advance by individuals who have no knowledge of efficacy results. Approximately eight weeks prior to each of these meetings, the database is locked in order to prepare a progress report. If the prerequisite number of patients evaluated for response has been attained, an interim analysis is also prepared and presented to the DSMB at their next scheduled meeting. The decision to terminate accrual to any particular regimen includes consideration of adverse events, treatment compliance and results from external studies. Additionally, the GOG Safety Review Committee (SRC) reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports on an ongoing basis (not efficacy results). This committee also reviews those deaths in which the study treatment may have been a contributing cause. The SRC reports to the DSMB and may recommend study amendments pertaining to patient safety.

11.361 Delta value to reject H_0: $p_d - p_m < -0.0957$; that is, p_m is at least 9.57% greater than p_d.

11.362 Delta value to reject H_1: $p_d - p_m > 0.0457$; that is, p_m is at least 4.57% less than p_d.

11.4 Safety analyses

Patients adverse events will be captured by individual adverse event terms and grade defined by the NCI Common Terminology Criteria for Adverse Events

version 4. The maximum grade of any adverse event observed during active treatment period or within 4 weeks of completing study treatment for each eligible patient will be tabulated. The proportion of patients with a serious adverse event or reported Grade 3 or worse adverse event, regardless of attribution, will be compared between the treatment regimens using a chi-square test. Additionally, the frequency of any hospitalization while on study therapy, frequency of early study treatment discontinuation not due to complete response or treatment failure, number of patients who receive non-protocol therapy and number of patients who receive non-protocol multi-agent chemotherapy.

11.5 Quality of life analyses

The QOL objective for this study is to measure the difference in QOL between patients in each randomized study arms. The FACT-G scale will be used to measure the overall QOL and is considered the primary QOL endpoint. The FACIT supplemental items will be used to measure treatment-related symptoms. Analysis of the FACIT supplemental items and treatment disruption will be treated as exploratory.

The QOL assessment time points are scheduled with the intention to achieve maximum compliance; however, there is still a possibility of noncompliance especially for patients whose disease does not respond to study treatments. These patients might seek other therapies that might interfere with their compliance to the QOL assessments. In GOG #174, treatment with actinomycin-D was discontinued due to lack of response in about 5% of patients before 2 cycles of treatment ; another 14% before cycle 4 and 7% before cycle 6. Thus we expect 90% eligible patients will complete QOL assessment at 2nd assessment (prior to cycle 3), 80% at the 3rd assessment (prior to cycle 5), and 70% at the 4th assessment (prior to cycle 7). With a sample size of 365 eligible patients, this study will achieve at least 88% statistical power to detect an effect size of 0.4 at a significance level of 5% using a two-sided two-sample test. Assuming the standard deviation of the FACT-G score is 15.86 in both groups, an effect size of 0.4 corresponds to a difference of 6.3 points between the two groups, which is considered clinically important (MID)[26]. The statistical power could be higher than estimated if the correlations among the repeated measures are taken into account. A linear mixed model that accounts for the correlation among the repeated measures will be fitted for the FACT-G score adjusting for baseline score and other covariates. The patient-reported symptom measurement scores and treatment disruption on QOL will be summarized by treatment arms with the estimated means for continuous variables or frequency tables for categorical variables accompanied with 95% confidence intervals.

The 6 month follow-up assessment will be considered non-definitive since at that time point the QOL will likely capture a mixture of effects not directly related to the study therapy, e.g. patients whose disease does not respond will be treated with surgery, single agent and/or multiple agent chemotherapy; some

reproductive-aged patients may get pregnant; or study treatment may continue for 26 weeks.

11.6 Uterine Artery Pulsatility Index Analysis

Investigators at Charing Cross Hospital have assessed the association of uterine artery pulsatility index with resistance to single agent methotrexate treatment and reported that patients with persistent GTN, FIGO score 0-6, treated with methotrexate and UAPI≤1 had increased risk of treatment resistance regardless of FIGO score (referred to as WHO score in this protocol) and this increased risk was more pronounced in patients with a score of 6.[27, 28] In this study, the analysis of UAPI will focus initially on testing the statistical significance of UAPI (values ≤ 1 vs. > 1) and an interaction factor of UAPI and WHO score (UAPI ≤ 1 and WHO score = 6 vs. UAPI >1 or WHO score < 6). In the two previous studies 46%-51% of patients had a UAPI of ≤ 1 and 2-4% of patients had UAPI ≤ 1 and WHO score = 6. Given the small proportion of patients with UAPI ≤ 1 and WHO score = 6, statistical power for inference on the coefficient for the interaction term will be extremely limited for moderate effects. The model of treatment resistance will also include an indicator for treatment and a treatment by UAPI interaction term. The main effect term for WHO score is not expected to be related to resistance in univariate analyses since the range of scores is generally associated with similar risks of resistance but it will be included in the model, nonetheless, when the UAPI/WHO score interaction term is included. The treatment/UAPI interaction term will only be kept in the model if significant at the 20% level (two sided).

Additional analyses will report predictiveness curves [34] (with observed risk for assessing calibration) for UAPI with and without the interaction term, functions of sensitivity, specificity and risk, risk distribution by treatment outcome, and AUC from ROC analysis. These analyses will help to evaluate the predictive accuracy of UAPI when predicting resistance to standard single agent therapy.

Measurement of UAPI in this study will be optional since it requires use of Doppler ultrasonography. At this time the degree of participation in this component is unknown. This study does not specify *a priori* a threshold of risk to determine recommendation for treatment with single versus multi-agent chemotherapy. Given the optional nature of this secondary objective, this study will not provide a final recommendation on how to incorporate UAPI into the current prognostic index, but will either confirm or refute its prognostic significance.

11.7 Anticipated distribution of patients' race and ethnicity (all are female)

Ethnic Category		%
Hispanic or Latino	58	15
Not Hispanic or Latino	326	85
Ethnic Category: Total of all subjects	384	100
Racial Category		
American Indian or Alaskan Native	8	2
Asian	46	12
Black or African American	65	17
Native Hawaiian or other Pacific Islander	4	1
White	261	68
Racial Category: Total of all subjects	384	100

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APPENDIX I

F.I.G.O. 2000 staging criteria for gestational trophoblastic neoplasia[17]

A. Criteria for the diagnosis of post-hydatidiform mole trophoblastic neoplasia (GTN) based on the modified W.H.O. risk/prognosis scoring schema.

1. GTN may be diagnosed* when the plateau of human chorionic gonadotrophin (hCG) lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21.

2. GTN may be diagnosed* when there is a rise of hCG of 3 weekly consecutive measurements or longer, over at least a period of 2 weeks or more; days 1, 7, 14.

3. GTN is diagnosed when the hCG level remains elevated for 6 months or more.**

4. GTN is diagnosed if there is a histologic diagnosis of choriocarcinoma.

* The actual level of hCG or the amount of rise will be determined by the individual investigator.
** This may not apply for patients with unexplained low-level hCG without clinical or imaging evidence of GTN.

B. Investigative tools to diagnose metastases

1. Chest x-ray is appropriate to diagnose lung metastases and it is chest x-rays that are used for counting the number of lung metastases to evaluate the risk score.

2. Liver metastases may be diagnosed by ultrasound or CT scanning.

3. Brain metastases may be diagnosed by MRI or CT scanning.

C. F.I.G.O. staging schema for GTN

Stage I	Disease confined to the uterus
Stage II	GTN extends outside the uterus but is limited to the genital structures (adnexae, vagina, and broad ligament).
Stage III	GTN extends to the lungs with or without genital tract involvement.
Stage IV	All other metastatic sites.

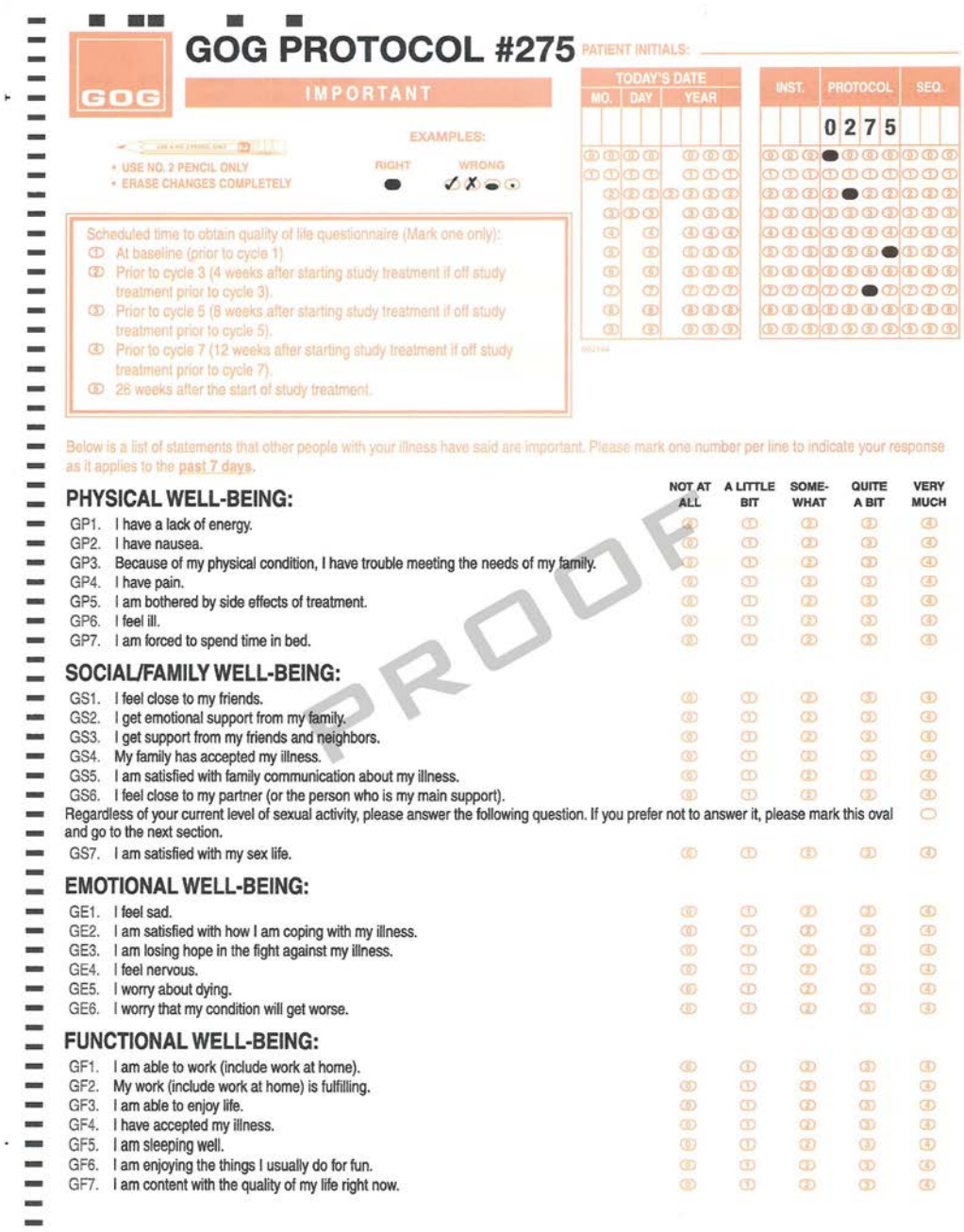
APPENDIX II

W.H.O. risk scoring criteria

Modified W.H.O. prognostic scoring system as adopted by F.I.G.O. (2000)[17]

Risk score	0	1	2	4
Age	< 40	40 or older	-	-
Antecedent pregnancy	mole	abortion	term	-
Interval months from index pregnancy	< 4	4 to < 7	7 to < 13	13 or more
Pre-treatment serum hCG (miu/ml)	$< 10^3$ (1 to 999)	10^3 to $< 10^4$ (1,000 to 9,999)	10^4 to $< 10^5$ (10,000 to 99,999)	10^5 or higher (100,000 and higher)
Largest tumor size including uterus	-	3 to < 5cm	5cm or larger	-
Sites of metastases	lung	spleen, kidney	gastrointestinal	liver, brain
Number of metastases	-	1 to 4	5 to 8	> 8
Previous failed chemotherapy	-	-	single drug	2 or more drugs

APPENDIX III



GOG PROTOCOL #275

PATIENT INITIALS: _____

IMPORTANT

- USE NO. 2 PENCIL ONLY
- ERASE CHANGES COMPLETELY

EXAMPLES: RIGHT ● WRONG ✓ ✗ ▬ ⊙

TODAY'S DATE			INST.	PROTOCOL	SEQ.
MO.	DAY	YEAR		0275	

Scheduled time to obtain quality of life questionnaire (Mark one only):
① At baseline (prior to cycle 1)
② Prior to cycle 3 (4 weeks after starting study treatment if off study treatment prior to cycle 3).
③ Prior to cycle 5 (8 weeks after starting study treatment if off study treatment prior to cycle 5).
④ Prior to cycle 7 (12 weeks after starting study treatment if off study treatment prior to cycle 7).
⑤ 26 weeks after the start of study treatment.

Below is a list of statements that other people with your illness have said are important. Please mark one number per line to indicate your response as it applies to the **past 7 days**.

	NOT AT ALL	A LITTLE BIT	SOME-WHAT	QUITE A BIT	VERY MUCH
PHYSICAL WELL-BEING:					
GP1. I have a lack of energy.	①	①	②	③	④
GP2. I have nausea.	①	①	②	③	④
GP3. Because of my physical condition, I have trouble meeting the needs of my family.	①	①	②	③	④
GP4. I have pain.	①	①	②	③	④
GP5. I am bothered by side effects of treatment.	①	①	②	③	④
GP6. I feel ill.	①	①	②	③	④
GP7. I am forced to spend time in bed.	①	①	②	③	④
SOCIAL/FAMILY WELL-BEING:					
GS1. I feel close to my friends.	①	①	②	③	④
GS2. I get emotional support from my family.	①	①	②	③	④
GS3. I get support from my friends and neighbors.	①	①	②	③	④
GS4. My family has accepted my illness.	①	①	②	③	④
GS5. I am satisfied with family communication about my illness.	①	①	②	③	④
GS6. I feel close to my partner (or the person who is my main support).	①	①	②	③	④
Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this oval and go to the next section.					○
GS7. I am satisfied with my sex life.	①	①	②	③	④
EMOTIONAL WELL-BEING:					
GE1. I feel sad.	①	①	②	③	④
GE2. I am satisfied with how I am coping with my illness.	①	①	②	③	④
GE3. I am losing hope in the fight against my illness.	①	①	②	③	④
GE4. I feel nervous.	①	①	②	③	④
GE5. I worry about dying.	①	①	②	③	④
GE6. I worry that my condition will get worse.	①	①	②	③	④
FUNCTIONAL WELL-BEING:					
GF1. I am able to work (include work at home).	①	①	②	③	④
GF2. My work (include work at home) is fulfilling.	①	①	②	③	④
GF3. I am able to enjoy life.	①	①	②	③	④
GF4. I have accepted my illness.	①	①	②	③	④
GF5. I am sleeping well.	①	①	②	③	④
GF6. I am enjoying the things I usually do for fun.	①	①	②	③	④
GF7. I am content with the quality of my life right now.	①	①	②	③	④

APPENDIX IV **(03/11/2013)**

Leucovorin Calendar

Patient Name: _____ Patient Study ID _____ Date: _____ /_____ / _____
This is a calendar to help you track when to take your Leucovorin pill and when you have taken it. Each time you return to your treatment center or doctor's office for the next injection, please bring this calendar with you.

When should you take your Leucovorin pill?
When taking Leucovorin, it should be taken between 24 & 30 hours after your injection of methotrexate. For example, if you are injected on Monday at 10 am, then you should take 1 Leucovorin (15mg) pill on Tuesday between 10am & 4pm.

What if you forget to take your pill?
If you forgot to take your Leucovorin pill on Tuesday between 10 am & 4pm, you should take the missed pill as soon as you remember if there is at least 12 hours before your next scheduled injection time. If there is less than 12 hours before your next injection time, then skip that pill. For example, you remembered your missed pill at 8 pm and you are scheduled to get your next methotrexate injection on Wednesday morning at 10 am. Because there are more than 12 hours before your next injection, you should take the missed pill.

Injection Day 1 ___/___/___	Leucovorin Day 2 ___/___/___	Injection Day 3 ___/___/___	Leucovorin Day 4 ___/___/___	Injection Day 5 ___/___/___	Leucovorin Day 6 ___/___/___	Injection Day 7 ___/___/___	Leucovorin Day 8 ___/___/___
Time Injected	Window to Take Pill	Time Injected	Window to Take Pill	Time Injected	Window to Take Pill	Time Injected	Window to Take Pill
AM PM	____ - ____	AM PM	____ - ____	AM PM	____ - ____	AM PM	____ - ____
	Time Pill Taken		Time Pill Taken		Time Pill Taken		Time pill taken
	AM PM		AM PM		AM PM		AM PM