

**UNIVERSITY OF ROCHESTER CANCER CENTER
CCOP RESEARCH BASE**

**Prevention of Delayed Nausea
A Phase III Double-Blind Placebo-Controlled Clinical Trial**

NCI protocol URCC 0402
URCC U1105

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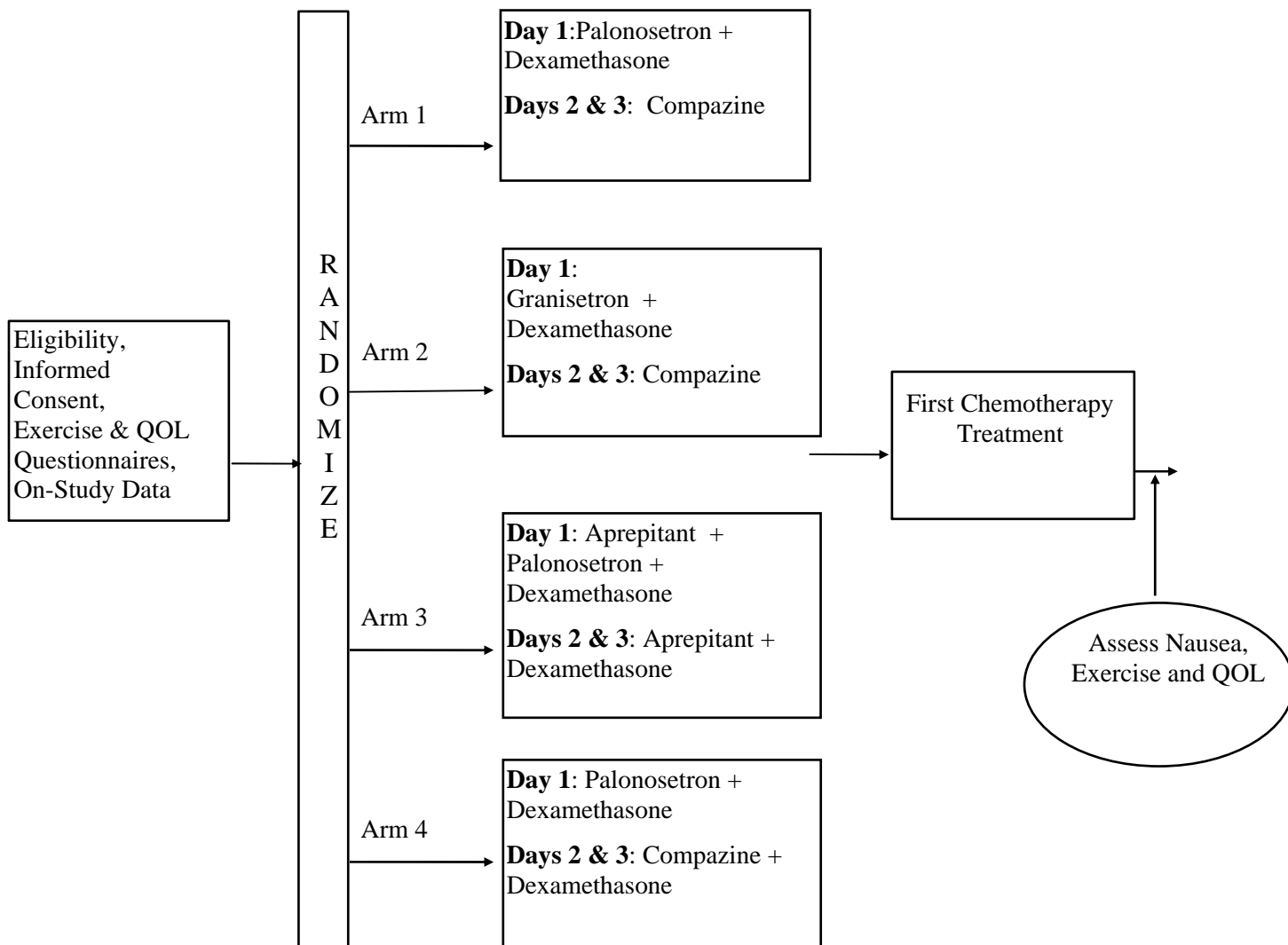
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Study Schema

(See Section 6.0 for details about the medication schedules and use of placebos to maintain blinding.)



1.0 Introduction

Over the last several years, delayed nausea has emerged as the “bête noire” of cancer chemotherapy. Despite the widespread use of first generation serotonin receptor antagonists, dexamethasone and a variety of other antiemetic medications, delayed nausea has continued to occur with nearly twice the frequency as acute nausea after treatment with highly (e.g. cisplatin) and moderate-to-highly (e.g. doxorubicin, epirubicin) emetogenic chemotherapy agents. Nausea and vomiting, besides being inherently unpleasant in and of themselves, can impact patients’ ability to complete everyday tasks, limit patients’ enjoyment of life, and, if severe, lead to medical complications such as anorexia, dehydration, electrolyte imbalance and esophageal tears, events that sometimes result in hospitalization. Elimination of these noxious side effects of chemotherapy can be expected to result in parallel improvements in cancer patients’ quality of life.

2.0 Background

In late 2003, we reported the results from a URCC CCOP study of chemotherapy-naïve patients enrolled in a study testing the ability of an information intervention to reduce nausea (U3996). Patients were being treated with regimens containing either cisplatin, carboplatin or doxorubicin and all received a 5-HT₃ receptor antagonist (ondansetron) with dexamethasone on the day of treatment, whichever antiemetic regimen comprised standard care at each participating CCOP practice site on the days following chemotherapy, and were allowed to take any additional treatments needed for control of symptoms caused by the cancer or its treatment on the days following chemotherapy. Nearly three quarters of the 322 patients who provided data at cycle one (73%) felt nauseated at some time during the delayed period and the proportion (68%) was similar for the 300 patients with data at cycle two. At both cycles, more than one-third (36%) experienced nausea only during the delayed period and 18% of the patients did not experience nausea until the third day of the cycle or later. Fifty-five described their delayed nausea as of moderate or greater intensity compared to 28% for acute nausea. Differences in delayed nausea frequency between doxorubicin and cisplatin were not significant with 75% of 47 treated with cisplatin and 83% of 169 treated with doxorubicin reporting some nausea at some point during the 5-day assessment period ($p = 0.21$).¹

Recently, we completed accrual to U3901, “Delayed Nausea-What Works Best?” Six hundred ninety-one patients were accrued to this three-arm study. All were chemotherapy-naïve and receiving their first course of chemotherapy containing doxorubicin (any dose; no liposomal doxorubicin or cisplatin) without concurrent radiation treatment or interferon. All received a short-acting 5-HT₃ receptor antagonist antiemetic with dexamethasone or the equivalent dose of methylprednisolone on the day of treatment (Day 1 of chemotherapy). Patients were then

randomly assigned to receive one of three antiemetic regimens on Days 2 and 3 of chemotherapy cycle one:

- Arm 1** Compazine (prochlorperazine) 10 mg p.o. three times daily (q 8 h)
- Arm 2** Any 5-HT₃ antiemetic using standard dosing regimens
- Arm 3** Compazine (prochlorperazine) 10 mg p.o. as needed for nausea

The key findings of that study are as follows.

Acute Nausea

Just over one-half of the patients in each arm had nausea on the day of treatment. There were no significant differences by study arm in the frequency of nausea or in mean or peak nausea severity on the day of treatment (acute post-chemotherapy nausea), indicating that the randomization procedure effectively insured that patients in the three arms were comparable with respect to nausea on the day of treatment, and also were at comparable risk for delayed symptoms, since occurrence of acute symptoms is the most important predictor of the subsequent development of delayed symptoms

Delayed Nausea

Significant differences by study arm were found in the frequency of delayed nausea (DN) on Days 2 and 3 of cycle 1. A smaller proportion of patients assigned to Arm 1 (Compazine q8h) had DN (71%) compared to patients assigned to the other two arms (Arm 2 [5-HT₃] 79%; Arm 3 [Compazine p.r.n.] 82%). There were significant differences in the frequency of DN between Arms 1 (Compazine q8h) and 3 (Compazine p.r.n.) ($p = 0.009$) and between Arms 1 (Compazine q8h) and 2 (5-HT₃) ($p = 0.05$). The difference in DN frequency between Arms 2 (5-HT₃) and 3 (Compazine p.r.n.) did not reach statistical significance.

There were no significant differences by study arm in mean delayed nausea severity or peak delayed nausea severity. This lack of difference in DN severity between groups was seen in spite of the fact that patients assigned to the 5-HT₃ arm took significantly more rescue medication on Days 2 and 3 than patients in either of the other 2 arms (see details below).

For all patients together, mean nausea severity was significantly greater during the delayed period (2.3; range 1-7) than on the day of chemotherapy (2.0) (paired samples t-test; $t = 6.227$, 666 df; $p < 0.001$). Also, for all patients together, peak nausea severity was significantly greater during the delayed period (3.5; range 1-7) than on the day of chemotherapy (2.6) (paired samples t-test; $t = 10.775$, 666 df; $p < 0.001$). Patients in all three groups had a significant amount of delayed nausea as indicated by maximum nausea severity on Days 2-3 = 3.4. (Arm 1; Compazine q8h), 3.5 (Arm 2; 5-HT₃) and 3.6 (Arm 3; Compazine p.r.n). (Range 1-7, with 1 = no nausea).

Vomiting

There were no significant differences by study arm in the proportion of patients who vomited either on the day of treatment or during the delayed period. A significantly greater proportion of patients vomited at least once during the delayed period (29%) than vomited at

least once on the day of chemotherapy (18%) (paired samples t test $t = 5.870$, 666 df, $p < 0.001$), although there was little delayed vomiting in any group (less than 1 episode per day).

Rescue Medication

The use of rescue medications varied significantly ($p < 0.001$) between the three study groups with 21% of patients in Arm 1, 34% in Arm 2, and 19 % in Arm 3 taking an additional medication (other than dexamethasone) to control symptoms on Days 2 and 3. For patients in the Compazine arms (Arms 1 or 3), these could include a 5-HT₃ antiemetic, Reglan, or a different antiemetic medication, while for patients in Arm 2 (5-HT₃, rescue medications could include Compazine, Reglan or another antiemetic drug. Significantly more patients on the 5-HT₃ arm took rescue medications than patients on either of the two Compazine arms.

Quality of Life

There were no differences in post-treatment QOL (FACT-B), or change in QOL from pre-treatment to post-treatment between the 3 arms.

Conclusion and plan for follow-up study

It seems clear from the data presented that none of these three regimens is adequate to control delayed nausea. At least three-quarters of all patients experienced nausea on days two and three of their first chemotherapy cycle. In particular, first generation 5-HT₃ antiemetics, used in the delayed period, were not any more effective against either mean or peak delayed nausea severity than Compazine. It is clear that better prevention and treatment of delayed chemotherapy-associated nausea is needed.

While this study was being conducted, two new antiemetics were approved by the FDA and introduced into oncology clinical practice. They have already been included in some published antiemetic guidelines (NCCN v1.2004, MASCC 2004). Initial registration trials suggest that these drugs, aprepitant (Emend®, Merck and Co., Inc., West Point, PA), an NK-1 receptor antagonist, and palonosetron (Aloxi™, MGI Pharma, Inc. Bloomington, MN), a unique second-generation selective serotonin 3 receptor antagonist with a much higher binding affinity for the 5HT3 receptor and an approximately 40 hour half life, improve the control of nausea and vomiting beyond that provided by previously-used regimens.

Palonosetron has been approved by the FDA for the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic chemotherapy as well as for the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy. Results of registration trials indicated that palonosetron is equally as or more efficacious than first generation serotonin receptor antagonists against both acute and delayed symptoms.²⁻⁴ Palonosetron is the first and only 5HT3 receptor antagonist to have a specific indication for prevention of delayed CINV in patients receiving moderately-emetogenic chemotherapy.

Aprepitant has been approved by the FDA and has been shown to improve the control of acute and delayed nausea and vomiting, particularly delayed symptoms, caused by high-dose cisplatin-based chemotherapy, when used together with a selective serotonin receptor antagonist (5HT3 RA) and dexamethasone.⁵⁻⁷ The role of the NK-1 pathway in high-dose cisplatin is clear,

and aprepitant, a selective NK-1 receptor antagonist, leads to approximately a 20 % improvement in complete response (CR; no emesis and no use of rescue therapy) over the 120 hour interval after chemotherapy, with clinically and statistically superior CR rates on day 1 (~15%) and 24-120 hrs (~15-20%) compared with a first generation 5HT3-RA plus dexamethasone on day 1 followed by dexamethasone on days 2-4. The role of aprepitant in non-cisplatin moderately emetogenic chemotherapy is less important: CR rates over the 0-120 hr interval after AC- chemotherapy in women with breast cancer was 51% compared to 42% for the standard of care regimen. There was no significant improvement in the delayed 24-102 hr CR rate (55%) for women receiving the aprepitant regimen, (Ondansetron 8mg bid day 1 plus dexamethasone 12 mg day 1 plus aprepitant 125 mg day 1 followed by aprepitant 80 mg days 2&3) compared with women receiving standard of care (49%), P>0.05 (Ondansetron 8 mg BID day 1 plus dexamethasone 20 mg followed by ondansetron 8 mg BID days 2-3).⁸

Rev 2/09 It seems both prudent and desirable to test these new medications in community-based oncology practices. This research will build on the results of our previous study in which we found that prochlorperazine (Compazine®) given by mouth in a dose of 8 mg three times daily was the most effective treatment arm for DN. The study will also test whether the addition of dexamethasone provides further benefit. Our previous study was limited to chemotherapy-naïve patients receiving doxorubicin but was not limited in regard to diagnosis.

Summary

Rev 2/09 Nausea, especially delayed nausea, is a significant problem for patients receiving emetogenic chemotherapy for cancer. Available guidelines generally agree with respect to prophylaxis for emesis. However, there is variation among guidelines, and the degree of confidence is lower, regarding regimens for the prevention of delayed nausea. With the FDA approval of and the introduction into clinical practice of the two new antiemetics described earlier, some antiemetic guidelines for highly and moderately emetogenic chemotherapy have recently been updated and now include the use of palonosetron (Aloxi™) a unique serotonin receptor antagonist along with dexamethasone on the day of chemotherapy. The addition of aprepitant (Emend®) to the regimen on Days 1-3 is suggested to prevent nausea, including DN, for “select patients” receiving highly and moderately emetogenic regimens. (National Comprehensive Cancer Network: Clinical Practice Guidelines in Oncology-Antiemesis Version 1.2004).

Rev 2/09 We are a long way from achieving the goal of eliminating nausea and vomiting from chemotherapy for all patients. Additional research to determine the optimal antiemetic regimen for the prophylactic control and treatment of delayed nausea could benefit patients significantly. We propose to conduct a randomized, double blind, placebo-controlled Phase III clinical intervention trial comparing the efficacy of four antiemetic regimens for the prevention and treatment of chemotherapy-related delayed nausea in patients being treated with chemotherapy regimens containing cisplatin, carboplatin, oxaliplatin or an anthracycline. The primary outcome will be the severity of delayed nausea following the first cycle of chemotherapy.

The study design is as follows:

Day 1

Arm 1	Palonosetron 0.25 mg I.V.	+ Dexamethasone 20 mg I.V.	+ Placebo ¹ p.o.
Arm 2	Granisetron 1 mg I.V.	+ Dexamethasone 20 mg I.V.	+ Placebo ¹ p.o.
Arm 3	Palonosetron 0.25 mg I.V.	+ Dexamethasone 12 mg I.V.	+ Aprepitant 125 mg p.o.
Arm 4	Palonosetron 0.25 mg I.V.	+ Dexamethasone 20 mg I.V.	+ Placebo ¹ p.o.

¹ This placebo will be made to exactly match Aprepitant 125 mg in appearance, taste and smell.

Days 2 and 3**

	AM	Mid-day	Evening
Arm 1	Compazine ² 10 mg p.o. + Placebo ³	Compazine ² 10 mg p.o.	Compazine ² 10 mg p.o.
Arm 2	Compazine ² 10 mg p.o. + Placebo ³	Compazine ² 10 mg p.o.	Compazine ² 10 mg p.o.
Arm 3	Aprepitant ² 80 mg p.o. + Dexamethasone 8 mg p.o.	Placebo ²	Placebo ²
Arm 4	Compazine ² 10 mg p.o. + Dexamethasone 8 mg p.o.	Compazine ² 10 mg p.o.	Compazine ² 10 mg p.o.

² Compazine 10 mg, aprepitant 80 mg, and a capsule containing only placebo will all be made to look, taste and smell exactly alike.

³ This placebo will be made to exactly match dexamethasone 8 mg in appearance, taste and smell.

** patients will take the same assigned medications on both days

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Our proposed study is designed to answer three principal research questions about control of nausea in patients receiving chemotherapy containing cisplatin, carboplatin, oxaliplatin or an anthracycline: 1) Does the addition of dexamethasone to prochlorperazine (Compazine®), given by mouth in a dose of 10 mg three times daily (approximately every 8 hours) on Days 2 and 3, result in better control of delayed nausea than the same dose of prochlorperazine (Compazine®) without dexamethasone? (Arm 1 vs. Arm 4) 2) Is palonosetron given with dexamethasone on the day of chemotherapy more effective than a first generation 5-HT₃ receptor antagonist (Kytril [granisetron], Roche Laboratories, Inc., Nutley, NJ) given with dexamethasone? (Arm 1 vs. Arm 2) 3) Is the currently recommended NCCN antiemetic guideline of an NK-1 receptor antagonist (aprepitant) combined with palonosetron (palonosetron) and dexamethasone on the day of chemotherapy the most effective antiemetic regimen for control of delayed nausea in patients receiving chemotherapy containing an cisplatin, carboplatin, oxaliplatin or an anthracycline? (Arm 3 vs. Arm 4).

Primary outcome variables will be delayed nausea severity and interference with functioning caused by nausea or emesis. As part of the study, we will ask participants to record whether metoclopramine, the “rescue” medication, was taken. We will gather information on participant characteristics known to be correlated with treatment-induced NV (i.e., age, history of morning sickness, nausea expectations and history of motion sickness) for later exploratory analyses and use as control variables as appropriate. In addition, we will record from each participant’s medical record height and weight to calculate body mass index and the dose (mg/m²

and total dose) of doxorubicin and epirubicin administered for preliminary correlation analyses about a possible relationship between obesity and chemotherapy dosing.

Several other factors that could have a role in the development of nausea will also be explored, including levels of physical exercise typically engaged in, as well as degree of fatigue and sleep disturbance at baseline and during the days following administration of chemotherapy. Physical exercise, which results in substantial physiological and psychological changes, is receiving increased attention in cancer control research. One randomized, controlled trial of 42 patients receiving chemotherapy for stage II breast cancer demonstrated significant improvements in nausea among the patients assigned to an exercise condition (3x/wk, WAIT protocol, 10wks), but not among those assigned to a stretching and conversation placebo intervention or a usual care control condition.¹⁰ Anecdotal evidence suggests that fatigue may be related to nausea; some individuals experience feelings of nausea and may even vomit under conditions of excessive fatigue. Degree of fatigue will be measured at baseline and on Day 4 of the on-study chemotherapy cycle using the Brief Fatigue Inventory (BFI) and fatigue will also be assessed daily along with sleep and exercise on the 4-Day Home Record. These measures will provide data for preliminary analyses about a potential relationship between these variables and chemotherapy-induced nausea. The degree to which nausea and emesis interfere with patients' ability to function and their sense of well-being will be assessed using the Osoba Nausea and Emesis Module.

3.0 Objectives

3.1 Primary Objectives

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3.1.1 To determine if the most effective treatment regimen for controlling treatment-related delayed nausea from our prior study, i.e., Compazine taken regularly three times daily on Day 2 and Day 3 of chemotherapy, can be enhanced by the addition of dexamethasone on those two days. (Arm 1 versus Arm 4)

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3.1.2 To determine if palonosetron is more effective than granisetron in controlling treatment-related delayed nausea. (Arm 1 versus Arm 2)

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3.1.3 To determine if the currently recommended¹¹ antiemetic guideline of an NK-1 receptor antagonist (aprepitant) combined with palonosetron and dexamethasone is the most effective antiemetic regimen for controlling treatment-related delayed nausea. (Arm 3 versus Arm 4).

3.2 Secondary Objectives

3.2.1 To determine if the addition of dexamethasone to Compazine taken regularly three times daily on Day 2 and Day 3 of chemotherapy is more effective than the same regimen without dexamethasone for reducing interference with functioning

caused by chemotherapy-induced nausea and vomiting (CINV). (Arm 1 versus Arm 4)

3.2.2 To determine if palonosetron is more effective than granisetronin for reducing interference with functioning caused by CINV. (Arm 1 versus Arm 2)

3.2.2 To determine if the currently recommended antiemetic guideline of an NK-1 receptor antagonist (aprepitant) combined with palonostetron and dexamethasone is the most effective antiemetic regimen for reducing interference with functioning due to CINV. (Arm 3 versus Arm 4)

Exploratory Objective

3.3.1 To examine the potential relationship between sleep quality, physical exercise, fatigue and chemotherapy-induced nausea.

4.0 Participant Eligibility

Study participants must:

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4.1 Have a diagnosis of cancer and be chemotherapy naive.

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4.2 Be scheduled to receive a chemotherapy treatment containing cisplatin (any dose or schedule), carboplatin (any dose or schedule), oxaliplatin (any dose or schedule), doxorubicin (any dose or schedule) or epirubicin (any dose or schedule), without concurrent radiotherapy or interferon treatment.

4.2.1 Chemotherapy may be for adjuvant, neoadjuvant, curative or palliative intent.

4.2.2 Dose-dense regimens (e.g. chemotherapy with doxorubicin or epirubicin given every two weeks) are allowed.

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4.2.3 For the purposes of this study, Day 1 of chemotherapy will be defined as the day of administration of cisplatin, carboplatin, oxaliplatin, doxorubicin or epirubicin.

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4.2.4 Regimens with multiple-day doses of doxorubicin, epirubicin, cisplatin, carboplatin, oxaliplatin, dacarbazine, hexamethylmelamine, nitrosoureas, or streptozocin are not allowed. Chemotherapy agents, other than those listed above, may be given orally, intravenously, or by continuous infusion on one or multiple days.

4.2.5 Regimens containing liposomal doxorubicin or cisplatin are not allowed.

- 4.3 Must not have clinical evidence of current or impending bowel obstruction or symptomatic brain metastases.
- 4.4 Must not be currently taking pimozone (Orap™), terfenadine (Seldane; not commercially available in the US), astemizole (Hismanal; withdrawn from market in the US) or cisapride (Propulsid®).
- 4.5 Be able to understand English (all assessment instruments are in English).
- 4.6 Be 18 years of age or older.
- 4.7 Give informed consent.

5.0 Registration and Randomization

- 5.1 Prior to entering participants on this protocol, the following must be on file at the URCC CCOP Research Base:
 - Documentation of IRB approval in the form of an HHS Form 310, CTSU approval form or signed letter from IRB
 - A copy of the institution's IRB-approved informed consent document
 - Written justification for any substantive modifications made to the informed consent concerning information on risks or alternative procedures.

These documents are submitted to:

Ms. Jacque Lindke
James P. Wilmot Cancer Center
URCC CCOP Research Base
601 Elmwood Av, Box 704
Rochester, NY 14642

- 5.2 To enroll a participant who meets the eligibility criteria and who has signed the informed consent document, either:
 - log on to the URCC CCOP Research Base website at <http://extranet.urmc.rochester.edu/ccop/>, enter your CCOP's username and password and enter the information outlined in section 5.3 below, or
 - call the University of Rochester Cancer Center at (585) 275-6303 between 8.30 AM and 4.30 PM on weekdays to verbally give the URCC registrar the information in section 5.3.
- 5.3 The following information will be requested:

- 5.3.1 CCOP site
- 5.3.2 Most recent IRB approval date
- 5.3.3 Name and telephone number of person registering study participant
- 5.3.4 Eligibility verification. Participants must meet all eligibility requirements listed in Section 4.0.
- 5.3.5 Primary chemotherapy drug (cisplatin, carboplatin, oxaliplatin, doxorubicin or epirubicin)
- 5.3.6 Verification that consent form has been signed
- 5.3.7 Treatment facility (coincides with IRB approval)
- 5.3.8 Participant's identification
 - 5.3.8.1 First and last names or initials
 - 5.3.8.2 Birth date (MM/DD/YYYY)
 - 5.3.8.3 Gender
 - 5.3.8.4 Race
 - 5.3.8.5 Nine-digit zip code
 - 5.3.8.6 Payment code

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5.3.9 Diagnosis

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5.4 An email confirmation of registration will be forwarded by the URCC, and if requested, a faxed confirmation to the CCOP's coordinating center.

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5.5 Participants will be stratified by CCOP site and by gender. Within each site and gender, a computer-generated random numbers table with block size two for each of the five levels of treatment (cisplatin, carboplatin, oxaliplatin, doxorubicin, epirubicin) will be used to assign participants to one of the four treatment arms. The random numbers tables will be generated centrally using Statistical Analysis System (SAS) software.

The four arms are as follows:

Arm 1 = Palonosetron & Dexamethasone on Day 1; Compazine on Days 2 & 3

Arm 2 = Granisetron & Dexamethasone on Day 1; Compazine on Days 2 & 3

Arm 3 = Palonosetron, Dexamethasone & Aprepitant on Day 1, Aprepitant & Dexamethasone on Days 2 & 3

Arm 4 = Palonosetron & Dexamethasone on Day 1; Compazine & Dexamethasone on Days 2 & 3

5.6 The randomization will assign participants to the four arms in the ratio 1:1:1:1.

6.0 Treatment Protocol, Study Outline

- 6.1 This is a randomized, double-blind, placebo-controlled Phase III clinical intervention trial to assess the efficacy of four distinct antiemetic regimens for the prevention of chemotherapy-induced delayed nausea (defined as any nausea occurring subsequent to the day of treatment). Details of the study design are as follows.

Day 1

Arm 1	Palonosetron 0.25 mg I.V.	+ Dexamethasone 20 mg I.V.	+ Placebo ¹ p.o.
Arm 2	Granisetron 1 mg I.V.	+ Dexamethasone 20 mg I.V.	+ Placebo ¹ p.o.
Arm 3	Palonosetron 0.25 mg I.V.	+ Dexamethasone 12 mg I.V.	+ Aprepitant 125 mg p.o.
Arm 4	Palonosetron 0.25 mg I.V.	+ Dexamethasone 20 mg I.V.	+ Placebo ¹ p.o.

¹ This placebo will be made to exactly match Aprepitant 125 mg in appearance, taste and smell.

Days 2 and 3

	AM	Mid-day	Evening
Arm 1	Compazine ² 10 mg p.o. + Placebo ³	Compazine ² 10 mg p.o.	Compazine ² 10 mg p.o.
Arm 2	Compazine ² 10 mg p.o. + Placebo ³	Compazine ² 10 mg p.o.	Compazine ² 10 mg p.o.
Arm 3	Aprepitant ² 80 mg p.o. + Dexamethasone 8 mg p.o.	Placebo ²	Placebo ²
Arm 4	Compazine ² 10 mg p.o. + Dexamethasone 8 mg p.o.	Compazine ² 10 mg p.o.	Compazine ² 10 mg p.o.

² Compazine 10 mg, aprepitant 80 mg, and a capsule containing only placebo will all be made to look, taste and smell exactly alike.

³ This placebo will be made to exactly match dexamethasone 8 mg in appearance, taste and smell.

Details of administration of medication are as follows.

6.2 Arm 1: Day 1- Before chemotherapy

6.2.1 Palonosetron (Aloxi™) will be administered as a single intravenous dose of 0.25 mg over 30 seconds approximately 30 minutes prior to chemotherapy.

6.2.2 Dexamethasone 20 mg will be administered intravenously and can be admixed with the palonosetron.

6.2.3 Placebo (to match 125 mg of aprepitant) will be given once by mouth.

Arm 1: Days 2 and 3

- 6.2.4 Each participant in this arm will take Compazine (prochlorperazine) 10 mg by mouth three times daily (approximately every 8 hours) with the first dose to be taken in the morning.
- 6.2.5 Each participant in this arm will also take one placebo (matching dexamethasone 8 mg) by mouth once daily in the morning, along with the first dose of Compazine.

6.3 Arm 2: Day 1-Before chemotherapy

- 6.3.1 Kytril (granisetron) 1 mg will be administered as a single intravenous dose over 30 seconds approximately 30 minutes, prior to chemotherapy.
- 6.3.2 Dexamethasone 20 mg will be administered intravenously, and can be admixed with the granisetron.
- 6.3.3 Placebo (to match 125 mg of aprepitant) will be given once by mouth

Arm 2: Days 2 and 3

- 6.3.4 Each participant in this arm will take Compazine (prochlorperazine) 10 mg by mouth three times daily (approximately every 8 hours) with the first dose to be taken in the morning.
- 6.3.5 Each participant in this arm will also take one placebo (matching dexamethasone 8 mg) by mouth once daily in the morning, along with the first dose of Compazine.

6.4 Arm 3: Day 1-Before chemotherapy

- 6.4.1 Palonosetron will be administered on the day of chemotherapy as a single intravenous dose of 0.25 mg over 30 seconds approximately 30 minutes prior to chemotherapy.
- 6.4.2 Dexamethasone 12 mg will be administered intravenously, and can be admixed with the palonosetron.
- 6.4.3 Aprepitant 125 mg will be given once by mouth.

Arm 3: Days 2 and 3

- 6.4.4 Each participant in this arm will take aprepitant 80 mg by mouth once in the morning.
- 6.4.5 Each participant in this arm will also take dexamethasone 8 mg once daily by mouth in the morning with aprepitant.

6.4.6 Each participant in this arm will also take two doses of placebo to match Compazine twice daily, one dose at midday and one dose in the evening.

6.5 Arm 4: Day 1-Before chemotherapy

6.5.1 Palonosetron will be administered on the day of chemotherapy as a single intravenous dose of 0.25 mg over 30 seconds approximately 30 minutes prior to chemotherapy.

6.5.2 Dexamethasone 20 mg will be administered intravenously, and can be admixed with the palonosetron.

6.5.3 Placebo (to match 125 mg of aprepitant) will be given once by mouth.

Arm 4 : Days 2 and 3

6.5.4 Each participant in this arm will take Compazine (prochlorperazine) 10 mg by mouth three times daily (approximately every 8 hours) with the first dose to be taken in the morning.

6.5.5 Each participant in this arm will also take dexamethasone 8 mg once daily by mouth in the morning with the Compazine.

6.6 Each patient will take 4 capsules total on Day 2 and Day 3: 2 capsules in the morning and then 1 capsule twice more, approximately 8 hours apart (i.e., mid-day and evening).

6.7 If nausea and/or vomiting persists, participants may take metoclopramide (Reglan[®]) in addition to the previously described regimens for control of nausea and vomiting on Day 2 and subsequent treatment days of cycle one.

7.0 Study Outline and Procedures

7.1 Patients must be approached for study participation before their first chemotherapy cycle.

7.2 Participant instructions and tasks:

7.2.1 Prior to (within two weeks of) the administration of the first chemotherapy treatment, participants will answer questions concerning their susceptibility to nausea, their expectations about experiencing nausea from chemotherapy, the amount of exercise they regularly engage in and complete the BFI and the Osoba Nausea and Emesis Module assessing their quality of life.

- 7.2.2 Participants will receive Day 1 antiemetic medications in the clinic as outlined in Section 6.1. These will be provided in a package with both intravenous and oral medications double blinded.
- 7.2.3 Each participant will be given a double blinded blister pack containing all of their assigned study medications for Days 2 and 3 of chemotherapy cycle 1, organized by day and time of day (morning, mid-day, evening) when the medications should be taken.
- 7.2.3.1 Each participant will take two capsules by mouth in the morning and one capsule at mid-day and one capsule in the evening for two consecutive days, starting on the morning of the day following receipt of doxorubicin or epirubicin (morning of Day 2 of cycle 1)
- 7.2.3.2 A missed dose of study drug may be taken if the time is within four hours of when the dose is customarily taken. Subsequent doses should be adjusted so they are evenly spaced out over the remaining waking hours until bedtime.
- 7.2.3.3 If the elapsed time since the missed dose is longer than four hours, that dose should not be taken and the next scheduled dose should be taken at the appropriate time.
- 7.2.3.4 Patients will be instructed to return their medication packs at the following chemotherapy cycle. The CRA will mark the location of any unconsumed pills on the Pill Count Form with Diagram.
- 7.2.4 Participants will be given a four-day diary to complete at home and mail back following their first chemotherapy treatment. In addition to assessing the occurrence and severity of nausea and the occurrence of vomiting, the diary will include questions about the use of metoclopramide (Reglan: the “rescue” medication), as well as the amount of exercise engaged in, ability to sleep and degree of fatigue experienced each day.
- 7.2.5 Participants will also complete the Osoba Nausea and Emesis Module, the Brief Fatigue Inventory and the Godin Leisure-Time Exercise Questionnaire on the third day after treatment (Day 4 of the cycle).
- 7.2.6 Participants will mail the completed questionnaires back to each site following their first chemotherapy treatment in postage-paid envelopes provided.
- 7.2.7 A phone call will be made to participants on the first, second or third day following treatment (Days 2, 3 or 4 of the cycle) to remind them to complete and mail back the questionnaires.

7.2.7.1 Day 4 is preferred for the call, however, if Day 4 falls on a weekend or holiday, the call may be made on the weekday corresponding most closely to Day 4.

7.3 Treatment Duration

7.31 The trial ends when the completed measures have been returned following the participant's first chemotherapy treatment.

7.4 Ancillary Treatments

7.4.1 The following ancillary treatments for control of symptoms caused by the cancer treatment may be administered as clinically indicated.

7.4.1.1 Ativan (lorazepam) 1 or 2 mg p.o. or I.V. for control of chemotherapy-related anxiety.

7.4.1.2 Reglan (metoclopramide) for additional control of persistent post-chemotherapy nausea and vomiting.

7.5 Adverse Event Reporting Requirements

7.51 No IND is required for this protocol. See section 8.4 for a list of expected side effects associated with each agent. The following guidelines should be used for reporting adverse events:

FOR EITHER UNEXPECTED OR EXPECTED EVENT	
GRADE 3	GRADES 4 and 5
Attribution of Possible, Probable or Definite	Regardless of Attribution
Expedited report within 10 working days. (Grade 1 & 2 Adverse Event expedited reporting NOT required.)	Expedited report within 10 working days. This includes all deaths within 30 days of the last dose of a study agent regardless of attribution. Any late death attributed to the agent (possible, probable, or definite) should be reported within 10 working days.

7.5.2 Adverse events can be submitted by mail to URCC at the following address:

Jacque Lindke
James P. Wilmot Cancer Center
URCC CCOP Research Base
601 Elmwood Avenue, Box 704
Rochester, NY 14642

Or by fax to Ms. Lindke at 585-461-5601.

7.5.3 The URCC CCOP Research Base Adverse Event (AE) Report will be used for submission of adverse events. Descriptions and grading scales from the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3 should be utilized when reporting AEs.

7.5.3.1 An *unexpected* adverse event is defined as any adverse drug experience, the specificity or severity of which is not consistent with the risk information described in section 8.0 below. As used in this definition, 'unexpected' refers to an adverse experience that has not been previously observed (i.e., included in the section 8.0 below) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

7.5.3.2 A *serious* event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.5.3.3 Associated with the use of the drug means that there is a reasonable possibility that the experience may have been caused by the drug.

7.5.3.4 Adverse events should be reported to the local IRB as per their requirements.

7.6 Data Safety and Monitoring

7.6.1 All adverse events requiring expedited reporting as outlined above will be reported to Jacque Lindke as described in section 7.5. These reports are entered into an electronic database and will be forwarded to Dr. Hickok, the URCC Data Safety and Monitoring Committee (DSMC) and University IRB for review.

- 7.6.2 Adverse event rates are monitored utilizing the electronic database. If an AE is found to be reported frequently, the Study Chair, Dr. Hickok, will conduct a detailed review. The DSMC Committee Chair will determine if further action is required.
- 7.6.3 The URCC DSMC will review study progress and cumulative reports of adverse events at annual meetings. An overall assessment of accrual, toxicities as described in the protocol, and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure.

8.0 Drug Characteristics, Dosage and Administration

8.1 Drug Formulation and Procurement

- 8.1.1 All study medications will be supplied. The study drugs will be packaged in separate kits to correspond to the individual protocols for Day 1 and Days 2 and 3 as described in section 6.0 for each of the four arms.

8.2 Storage and Stability

- 8.2.1 Drugs are stable at normal room temperatures (between 68° F and 77°F) and will be stored in a locked closet at the offices of the URCC CCOP Research Base. They will be distributed to the individual CCOPs from the Research Base.

8.3 Dosage and Administration

- 8.3.1 Drugs will be administered in the dosage and manner specified for each arm in section 6.0.

8.4 Side Effects

- 8.4.1 Compazine® (prochlorperazine) may cause drowsiness, dizziness or blurred vision. Caution should be used when driving or using machinery while taking this drug. Participants should avoid drinking alcohol while taking this drug. Rarely, involuntary movements of the body can develop, usually in persons taking Compazine in higher doses and for longer times than prescribed in this study.
- 8.4.2 The 5-HT₃ receptor antagonist antiemetic granisetron (Kytril®) can cause headaches, constipation or diarrhea.
- 8.4.3 The side effects of the long-acting 5-HT₃ receptor antagonist palonosetron (Aloxi™) are similar to those seen with first-generation serotonin receptor

antagonists and include headache, constipation and diarrhea. Dizziness, fatigue, abdominal pain and insomnia have been reported in 1% of patients or less. Although it is not recommended that palonosetron be administered on sequential days, daily dosing of 0.25 mg I.V. for three consecutive days (N = 12) did not result in any appreciable toxicity, except for one case of mild pruritis. (Data presented in a poster at the MASCC/ISOO 16th International Symposium: Supportive Care in Cancer, June 14-17, 2004, Miami, FL.)

8.4.4 Adverse reactions of the selective antagonist of the substance P/neurokinin 1 (NK₁) receptor, aprepitant, (Emend®) are uncommon and are usually of mild intensity. Abdominal pain, fatigue, hiccups, dizziness, diarrhea, epigastric discomfort, gastritis, nausea, anorexia have been reported more often in patients taking aprepitant than those without the drug.

8.4.4.1 Since aprepitant can lower INR levels if taken concurrently with warfarin, prothrombin times may need to be followed more closely in participants taking warfarin.

8.4.4.2 Sexually active participants who are relying on oral contraceptives to prevent pregnancy, should use a barrier method of contraceptive while participating in this research study.

8.4.5 Dexamethasone may cause nausea, vomiting, upset stomach, appetite change, edema (swelling of legs), headache, dizziness, mood swings and difficulty sleeping.

9.0 Treatment Evaluation

9.1 Measures

9.1.1 Nausea, for the primary outcome variable, will be measured by a self report diary developed by Burish¹² and Carey¹³ and completed by participants over a four-day period (Four-Day Home Record). Each day is divided into four segments (morning, afternoon, evening, night) and participants report the severity of nausea and whether or not they vomited for each period on the day of treatment and on the three following days (16 total reporting times). Severity of nausea is assessed on a 7-point semantic rating scale anchored at one end by "1" = "Not at all Nauseated" and at the other end by "7" = "Extremely Nauseated." Mean nausea severity scores will be calculated from the latter three reporting periods on Day 1 (for acute nausea) and from the 8 reporting periods from Days 2 & 3 (for delayed nausea). Day 4 data will be collected for exploratory purposes only. Anti-nausea medication use, exercise, severity of fatigue and degree of sleep disturbance will also be recorded for each day as part of the four-day record.

- 9.1.2 Quality of life will be assessed using the Functional Assessment of Cancer Therapy Scale-General (FACT-G; version 4).¹⁴ The FACT-G is a 28-item scale developed specifically for use in cancer clinical trials. It was developed through extensive interviews with patients experiencing symptoms of cancer and with oncology professionals and has been validated in a series of studies of 542 cancer patients. It has shown very good test-retest reliability as well as validity. Along with a total score representing QOL, there are psychometrically validated subscales of physical, functional, social, and cognitive-emotional status. It is easily administered (taking approximately 10 - 15 minutes) and has been found to be responsive to clinical change. We have used this scale in previous studies; thus, use in this study will allow comparison with results of our previous research.
- 9.1.3 Health-related quality of life will be assessed by addressing the impact of fatigue, nausea, and vomiting on patients' ability to function in their everyday lives. These aims will be accomplished by administering the Brief Fatigue Inventory and the Osoba Nausea and Emesis Module. The revised Brief Fatigue Inventory (BFI)¹⁵ is a 9-item instrument that allows for the rapid assessment of fatigue level in cancer patients and identifies those patients with severe fatigue. Three items ask patients to rate their fatigue for "now," and fatigue at its "worst" and "usual" for the last 24 hours. The 11-point scales are bounded by 0 = "no fatigue" and 10 = "fatigue as bad as you can imagine." Using the same type of scales, the remaining questions ask patients to rate how their fatigue interferes with several quality of life domains including general activity, walking, mood, work, and relations with others. These scales are bounded by 0 = "does not interfere" and 10 = "interferes completely." The reliability and validity of the BFI were demonstrated in a study of 305 cancer patients and 290 community-dwelling adults. An internal consistency coefficient (Cronbach's alpha) = 0.96 was demonstrated when the BFI was administered to 305 patients with cancer.¹⁵ The BFI will be scored by averaging the responses to the nine questions as recommended by Mendoza.¹⁵
- 9.1.4 The degree to which nausea and vomiting interfere with patients' ability to engage in their everyday activities will be assessed by administering the Osoba Nausea and Emesis Module (ONEM).¹⁶ The ONEM measures the short-term impact of nausea and emesis on patients' ability to function and their sense of well-being while receiving emetogenic chemotherapy. In a sample of 134 cancer patients receiving chemotherapy, internal consistency reliability as measured by Cronbach coefficient Alpha was 0.85, and test-retest reliability as measured by the intraclass correlation coefficient was 0.77. Convergent and discriminant validity as well as known-group validity were also demonstrated. The ONEM shows strong responsiveness-to-change scores. Higher scores indicate more interference. The scale will be given at baseline (within 2 weeks of beginning chemotherapy) and again on day 4.
- 9.1.5 The amount of leisure time spent in physical activity will be assessed using the Godin Leisure Time Exercise Questionnaire (GLTEQ).¹⁷ The GLTEQ consists of

two questions designed to assess the frequency within a typical 7 day week of mild, moderate, and strenuous exercise performed for a duration of at least 15 minutes during a participant's free time. The measure is easily administered and brief, with a retest coefficient of .62, a concurrent coefficient of .32 and an objective validity coefficient of .56 compared with CALTRAC accelerometry, estimated VO₂ max and body composition (via hydrostatic weight).¹⁸ The GLTEQ has also been used successfully in populations of adult cancer patients.¹⁹⁻²² The GLTEQ will be given three times, twice at baseline (once to assess exercise habits prior to the diagnosis of cancer and once to assess exercise habits since the diagnosis of cancer) and once on day 4 (to assess exercise habits during the four day period).

- 9.1.6 On-study data collected will include several participant and treatment variables for exploratory analyses and possible use as covariates. These include: type and dose of chemotherapy, demographic information, weight, height, participant's history of nausea from various causes, and expectations concerning the likelihood of experiencing nausea.

10.0 Statistical Considerations

- 10.1 The primary outcome variable for this study will be the severity of delayed nausea (measured four times daily on a 7-point rating scale anchored by "not at all nauseated" and "extremely nauseated") averaged across Days 2 & 3 of treatment. All analyses will be done on an intent-to-treat basis; participant data will be included in the treatment group to which the participant was randomized regardless of any subsequent changes to the treatment.
- 10.2 Preliminary analyses of data from our recent URCC CCOP Research Base protocol described earlier (NCI protocol 3901) suggests that the mean delayed nausea severity in participants receiving doxorubicin is 2.12 with a standard deviation of 1.29. The accrual goal for this study is 800 evaluable participants. To allow for 10% of randomized participants to fail in providing information about the outcome variables after their first chemotherapy treatment, a total enrollment of 890 participants is planned. 200 evaluable participants per group will provide 80% power to detect a 0.42 difference in mean nausea severity between any pair of conditions, at the 0.05 overall significance level, adjusting for the 3 comparisons we will make using the Bonferroni method. No interim analyses of the data are planned.
- 10.3 Data from U3901 "Treatment of Delayed Nausea: What Works Best?" show a mean change score of -3.67 from baseline for the FACT-G functional subscale, with a standard deviation of 5.36. 200 evaluable participants per group will provide 80% power to detect a difference of 1.73 in mean change score of this functional QOL measure between any

pair of arms, at the 0.05 overall significance level, adjusting for the 3 comparisons we will make using the Bonferroni method.

10.4 One-way ANOVA statistical technique will be used for the primary analysis, and contrast statements in one-way ANOVA will be used to compare the average nausea severity between each of the treatment arms. Since three comparisons will be made for the primary objectives, the significance level is set to be equal to $0.05/3=0.017$. This will allow the overall type I error of finding at least one significance result when the null hypotheses are true to be still less or equal to 0.05.

10.5 For the secondary QOL outcome measure, using the functional subscale of the FACT-G, we will calculate the change score between post- and pre-treatment measurements for each subject. ANCOVA statistical technique will be used on the change scores to test for overall difference between treatment groups, adjusting for the baseline functional measure. Contrast statements in ANCOVA will be used to compare each pair of arms. Since three comparisons will be made for the secondary objectives, the significance level is set to be equal to $0.05/3=0.017$.

Rev 2/09 10.6 Additional analyses for each outcome will use regression models to test for differences between treatment arms, while controlling for age, sex, race, whether or not the participant felt nauseous or vomited on Day 1 of chemotherapy, primary chemotherapy drug (cisplatin, carboplatin, oxaliplatin, doxorubicin or epirubicin), dose of primary chemotherapy drug, and histories of motion sickness and morning sickness during pregnancy. Terms representing interactions of treatment group with these participant factors will be added to test for possible differences in treatment effects across subgroups. Results of interaction tests will be considered exploratory only.

10.7 Exploratory regression analyses will also be used to examine the potential relationship between sleep quality, physical exercise, fatigue and chemotherapy-induced nausea.

10.8 Enrollment of the 890 participants is expected to take 36 months.

Rev 2/09 10.9 Representation of Women and Minorities. Based upon accrual patterns to URCC protocol 3996 which had similar eligibility criteria, we expect approximately 73% of accrued patients to be female. None of the eligibility criteria for the study involve ethnicity. Two Minority-Based CCOP members are affiliated with our group and all have expressed interest in participating in this protocol. Past enrollment in our CCOP studies has closely paralleled the ethnic composition of the available population.

11.0 Records To Be Kept

FORM	SCHEDULE OF DATA COLLECTION	
	Baseline ¹	After Chemotherapy Cycle 1
URCC Clinical Trial Patient Registration Form, Eligibility Checklist, Consent Form	X	
On Study Data/Participant Interview	X	
Godin Exercise Questionnaire²	X	X
Brief Fatigue Inventory²	X	X
Osoba Nausea and Emesis Module²	X	X
FACT-G²	X	X
Four-Day Home Record (NV, metoclopramide use, exercise, sleep, fatigue)		X
Participant Contact Sheet⁴		X
Chemotherapy Flow Sheet (copy from patient chart)		X
Height, Weight and Chemotherapy Dose Sheet		X
Pill Count Form with Diagram		X
Case Summary Form		X

¹ Before chemotherapy cycle 1.

² Completed at Baseline and on Day 4.

³ Completed on Day 4.

⁴ Contact participants on Day 4 to complete and return questionnaires.

- 11.1 All written materials will be kept confidential, locked in the private office of the research coordinator and identified only by ID numbers.

11.2 The Case Summary should accompany ALL data submissions. All completed forms must be submitted within 30 days of the first chemotherapy treatment and should be sent to:

Shonda Ranson
URCC CCOP Research Base
601 Elmwood Avenue, Box 704
Rochester, NY 14642

12.0 Participant Consent and Peer Judgment

All investigational, FDA, NCI, state, federal and institutional regulations concerning informed consent and peer judgment will be fulfilled.

13.0 References

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