

Official Study Title:

Randomized, placebo-controlled study of FOND (fosaprepitant, ondansetron, dexamethasone) versus FOND+O (FOND plus olanzapine) for the prevention of chemotherapy induced nausea and vomiting in hematology patients receiving highly emetogenic chemotherapy regimens: the FOND-O Study

NCT Number:

02635984

Document Date:

updated 7-11-2016

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Principal Investigator: Amber Clemmons, PharmD, BCOP

1. Objectives

The objective of this study is to compare the effectiveness of olanzapine added to standard triplet therapy (fosaprepitant, ondansetron, and dexamethasone) versus triplet therapy alone in preventing chemotherapy-induced nausea and vomiting (CINV) in hematology patients receiving highly or moderately emetogenic chemotherapy regimens.

The primary objective is to determine if addition of olanzapine to standard triplet therapy improved the complete response rate defined as no emesis and minimal nausea (< 25 mm on a 100 mm visual analog scale [VAS]) during the overall assessment period (starting day 1 of chemotherapy and continuing for 5 days after discontinuation of chemotherapy) for the first cycle of chemotherapy.

Secondary objectives will be reported as acute phase [chemotherapy days], delayed phase [5 days after chemotherapy administration], and overall phases [chemotherapy days plus 5 days after].

The secondary objectives are to determine if addition of olanzapine to standard triplet therapy:

- Reduces the number of emetic episodes per patient
- Reduces the number of rescue medication doses per patient
- Reduces the percent of patients with minimal nausea (<25 mm on a 100 mm VAS)
- Reduces the percent of patients achieving complete protection (CP = no emesis, no breakthrough antiemetic use, no significant nausea)

For safety analysis, an additional secondary objective will assess the rate of study drug (olanzapine or placebo) discontinuation.

2. Background

Nausea and vomiting remains a common and difficult to manage consequence of chemotherapy despite prophylaxis. These symptoms can often lead to a decreased quality of life, dehydration, and malnutrition.

Historically, patients have been prescribed dexamethasone along with a 5HT3 antagonist (ex: ondansetron) to prevent nausea and vomiting. For patients with highly and often moderately emetogenic chemotherapy, an NK1 receptor antagonist, such as fosaprepitant, is added to the regimen. Despite the use of these dual and triple agent preventative strategies as recommended by national guidelines (i.e., American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN]), nausea and vomiting remains a significant complication from chemotherapy.

Olanzapine is an FDA approved atypical antipsychotic that blocks multiple neuronal receptors involved in nausea/vomiting pathways¹. Olanzapine has been studied for breakthrough² chemotherapy-induced nausea and vomiting (CINV) as well as in prophylaxis of highly and moderately emetogenic regimens (HEC & MEC, respectively)^{3,4,5}. However, these studies have focused on patients with solid tumor malignancies and single day chemotherapy regimens. A phase I trial established the dose of olanzapine for CINV to be 10 mg daily⁶. In the earliest clinical trials, olanzapine was added to a 5HT3 antagonists and corticosteroid^{1,7} or compared to 5HT3 alone⁸ for preventing CINV with HEC and MEC regimens for a variety of solid tumors and lymphoma. These studies reported improved control of delayed nausea and vomiting with use of olanzapine. Additionally, olanzapine has been studied in replacement of NK1 receptor antagonists (i.e., aprepitant) as well as in addition to standard triplet prophylaxis regimens which include NK1 receptor antagonists^{4,5,6,7}. The results of these trials suggest olanzapine is at least as effective as aprepitant and combination olanzapine with aprepitant has led to promising reports of CINV control. Based on the results from these various studies, national guidelines (National Comprehensive Cancer Network [NCCN] guideline on Antiemesis version 1.2015) recommend olanzapine 10 mg PO daily as an option within prophylaxis regimens for HEC and MEC chemotherapy regimens. Further well-designed trials are warranted to define the optimal place in therapy for olanzapine (in replacement of or in combination to NK1 receptor antagonist) in HEC and MEC regimens, respectively.

To date, no publications have reported outcomes from adding olanzapine to standard triplet therapy^{9,10} specifically for hematology patients, including those receiving multi-day HEC and MEC regimens and/or undergoing hematopoietic stem cell transplants.

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6. Passik SD, Navari RM, Jung S, et al. Phase I trial of olanzapine for the prevention of delayed emesis in cancer patients: A Hoosier Oncology Group study. *Cancer Investigations* 2004; 22(3): 383-388.
7. Navari A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy induced nausea and vomiting: a Hoosier oncology group study. *Support Care Cancer* 2007; 15:1285-1291
8. Wang X, Wang L, Wang H, Zhang H. Effectiveness of olanzapine combined with ondansetron in prevention of chemotherapy-induced nausea and vomiting of non-small cell lung cancer *Cell Biochem Biophys* 2015; 72:471-473.
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10. Stiff PJ, et al. Prevention of nausea and vomiting associated with stem cell transplantation: results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. *BBMT E-pub ahead of print*: 31 July 2012. DOI: 10.1016/j.bbmt.2012.07.019.

3. Inclusion and Exclusion Criteria

Inclusion Criteria

18 years of age or older

Inpatient or outpatient hematology patient receiving one of the following regimens:

Chemotherapy for hematologic malignancy:

ABVD (Adriamycin 25mg/m², Bleomycin 10 units/m², Vinblastine 6mg/m², Dacarbazine 375mg/m² on days 1 and 15) *Outpatient Regimen*

ICE ± R (Rituximab 375mg/m² Day 1, Ifosfamide 5000mg/m² Day 2, Carboplatin AUC=5 Day 2, and Etoposide 100mg/m² Days 1-3) *Outpatient/Inpatient Regimen*

7+3 (Cytarabine 100-200mg/m² Days 1-7, Daunorubicin 60-90mg/m² Days 1-3)

Conditioning therapy for stem cell transplantation:

BEAM (Carmustine 300mg/m² on Day -6, Etoposide 200mg/m² Q12H on Days -5 to -3, Cytarabine 200mg/m² Q12H on Days -5 to -2, Melphalan 140 mg/m² on day -1)

Bu/Cy ± ATG (Busulfan 0.8mg/kg Q6H on Days -7 to -4, Cyclophosphamide 60mg/kg on days -3 to -2)

Bu/Flu ± ATG (Fludarabine 40mg/m² on days -6 to -3, Busulfan 130mg/m² on days -6 to -3)

FluCy ± ATG (Fludarabine 25mg/m² on days -5 to -1, Cyclophosphamide 50mg/m² on day -7 and -6)

FluCy + TBI (Fludarabine 40 mg/m² Days -6 to -2, Cyclophosphamide 50 mg/kg on Day -6, TBI on Day -1)

BuMel (Busulfan 3.2mg/kg on days -5 to -3, Melphalan 140mg/m² on day -2)

FluBuCy (Fludarabine 25mg/m² on days -6 to -2, Busulfan 130mg/m² on days -7 to -4, Cyclophosphamide 14.5 mg/kg on days -3 to -2 and 50 mg/kg on days +3 and +4)

Melphalan 140-200 mg/m² on day -1 *Outpatient Regimen*

Etoposide + TBI (Etoposide 60mg/m² on Day -3, TBI Day -7 to -4)

Cyclophosphamide + TBI (Cyclophosphamide 60mg/m² on Days -6 and -5, TBI Days -3,-2, and -1)

Note: All of the above listed regimens are highly or moderately emetogenic (HEC, MEC) per the National Comprehensive Cancer Network Antiemesis Guidelines 2015

Per physician discretion, outpatient regimens can be administered inpatient per Georgia Regent's normal operations. Additionally, the regimen descriptions above are general doses per the clinical studies; if a patient's dose is modified (renal adjustments, pharmacokinetic changes, etc.) they will not be excluded from taking part in this study.

Exclusion Criteria

Allergy to olanzapine

Documented nausea or vomiting ≤24 hours prior to enrollment

Treatment with other antipsychotic agents such as risperidone, quetiapine, clozapine, phenothiazine or butyrophenone ≤ 30 days prior to enrollment or planned during protocol therapy
Chronic alcoholism
Pregnant
Declined or unable to provide an informed consent

4. Number of Subjects/Records/Samples Collected

110 total patients will be accrued for this study to allow for 10% drop out or loss to follow up. See section below for description of sample size calculation.

5. Recruitment Methods

Describe when, where, and how potential subjects will be recruited

Patients will be identified by the clinical hematology/oncology pharmacists before a patient is initiated on one of the chemotherapy regimens listed in the inclusion criteria. Patients may be identified in the inpatient or outpatient setting through the chemotherapy patient lists which are part of routine practice at GRU for coordination of care. Once a patient is identified, he/she will be approached by a member of our study team to discuss consent. Additionally, there will be a study investigator present at each bone marrow transplant (BMT) intake meeting on Friday mornings. These meetings will allow the study investigators to identify patients to enroll and discuss the process with the hematology physicians prior to the patient being admitted. Note that the physician co-investigator on this study is the department head for the BMT program at GRU and is intimately involved in routine patient care for each subject who would be approached for this study.

Patients receiving outpatient chemotherapy will be approached by a member of the study team during their clinic visit prior to receiving chemotherapy. The study team member will be able to discuss the research protocol and informed consent document at that time.

Patients receiving inpatient chemotherapy will be approached by a member of the study team on the day of admission for chemotherapy or no later than the first day of chemotherapy for existing inpatient admissions. The study team member will be able to discuss the research protocol and informed consent document at that time in the patient's hospital room.

6. Procedures Involved

- a. *Describe the procedures involved to include those procedures that are standard evaluation and/or care and those that are solely for research purposes:*

All subjects will receive standard triplet antiemetic therapy which consists of ondansetron and dexamethasone on each day of chemotherapy plus fosaprepitant 150 mg IV once per national guidelines for CINV prophylaxis (see background section above). In addition to those antiemetics, subjects will be randomized to receive placebo or olanzapine 10mg orally on all chemotherapy days and for three additional days post chemotherapy in addition to standard triplet therapy. This dosing strategy mirrors prior studies of olanzapine in CINV

(see background above). The addition of olanzapine or placebo would be given solely for research purposes.

All study subjects will have access to the same rescue antiemetic medications as per standard medical care.

Assessment of vomiting via review of electronic medical records (intake/output record) and assessment of utilization of rescue antiemetic agents for CINV (review of medication administration record) is part of routine medical care/evaluation for all subjects. This assessment would not change for the participants of the study. Assessment of nausea is a standard medical evaluation for these patients as well via discussion with patients by the medical team; however, for this study the assessment tool (VAS form) will be utilized for study purposes only and would not routinely be filled out by patients not on the study.

b. Describe and explain the study design:

This is a blinded, placebo controlled trial randomizing patients to receive placebo or olanzapine 10 mg orally on all chemotherapy days plus three additional days post chemotherapy in addition to standard triplet therapy (ondansetron and dexamethasone on each day of chemotherapy and fosaprepitant 150 mg IV on day one of chemotherapy). See above for randomization procedure details.

Patients will be randomized to placebo or olanzapine in a block design stratified by chemotherapy type (transplant conditioning vs. chemotherapy only) and number of days of chemotherapy (single vs. multi-day) by the Investigational Drug Pharmacy services (IDS) at GRU Medical Center. The block randomization will occur in blocks of four and is blinded to all study investigators. The placebo tablets and olanzapine tablets will be packaged and classified by our IDS staff to ensure blinding of patients, nursing, and pharmacy staff including the study investigators. The placebo tablet is similar color and size as the study drug, olanzapine, to aid in effective blinding.

For study patients who are inpatient, each blinded dose of study drug/placebo will be dispensed from the IDS Pharmacy for administration by nursing staff. Therefore, assessment of adherence will be possible via review of the medication administration record (MAR) for these study patients. For study patients who are outpatient, the IDS Pharmacy will dispense the study drug/placebo as an outpatient prescription to be administered by the patient. Pill bottles will be collected at the standard of care return visit by study personnel for pill count to assess adherence.

Outcome measures assessed:

Primary: overall percentage of patients who had a complete response (CR) defined as no emesis and minimal nausea (< 25 mm on a 100 mm visual analog scale [VAS]) during the overall assessment period (starting day 1 of chemotherapy and continuing for 5 days after discontinuation of chemotherapy) for the first cycle of chemotherapy.

Secondary (all to be reported as acute [chemotherapy days], delayed [5 days after chemotherapy administration], and overall phases [chemotherapy days plus 5 days after])

- o Number of emetic episodes per patient
- o Number of rescue medications doses administered per patient
- o Percent of patients with no significant nausea (<25 mm on a 100 mm VAS)
- o Percent of patients achieving complete protection (CP = no emesis, no breakthrough antiemetic use, no significant nausea)
- o Rate of discontinuation of study drug

Nausea will be assessed in both the inpatient and outpatient settings using the visual analog scale (VAS). This is the standard assessment tool for CINV in previous trials. The VAS scores will be evaluated on the inpatient setting by study personnel, whereas the patient will be responsible for returning their VAS documentation in the outpatient setting at the standard of care follow-up visit. Each patient will be given a notebook that includes their VAS documents and instructions for returning the notebook. See Appendix A for an example of our study VAS document. This document will include a de-identified number for each study subject and no PHI.

NOTE: For patients receiving chemotherapy regimens (i.e. ABVD and ICE) that are administered for more than one cycle, only data from the first cycle will be included in the assessment of the primary outcome. During subsequent cycles, patients can elect to be unblinded and receive olanzapine; however, that data will only be included as a secondary analysis of outcomes during repeat chemotherapy cycles.

c. Describe the procedures performed to lessen the probability or magnitude of risks:

In regards to risk to the study subjects who are randomized to receive the study drug, olanzapine, all patients will be assessed for side effects per routine assessment during standard medical care. Inpatients are assessed daily by the hematology service and outpatients are assessed at follow-up visits by laboratory and physical assessment. Study investigators are directly involved in these daily direct patient care activities as part of their routine daily activities. Patients have access to the Cancer Center resources if any questions or concerns arise while outpatient. As for the risk to confidentiality, appropriate measures will be taken to safeguard patient data. All identifiable patient information will be stored on the institutional secure R drive in electronic format or locked in a secure file cabinet if in paper format. Only one document will be generated with the list of patient names and MRNs along with the random study number. This document will only be kept on the R drive and will not be transmitted electronically. All patient data will be collected on a de-identified electronic Excel document stored on the R drive.

d. Describe the duration of an individual subject's participation in the study and the time involved:

Each patient will be included from the start date of chemotherapy until 5 days post chemotherapy (range 6-11 days). Data will be stored until the final project manuscript is complete and data storage is no longer necessary. Subjects may withdraw at any time and no further data will be collected. However, subjects will continue to be followed by the

hematology team for standard of care purposes (i.e., non-research purposes) where ongoing safety monitoring can occur if necessary.

7. Data and Specimen Management

<p>a. <i>Describe the data analysis plan, including any statistical procedures:</i> Based on an 80% power and an alpha of 0.05, we estimated a need for 49 patients in each treatment arm. From a review of existing literature, the sample size is based on an estimated complete response achieved in 65% of patients on triplet therapy alone and a hypothesized clinically relevant increase of 25% for the treatment group to 90%. Therefore, 110 total patients will be accrued for this study to allow for 10% drop out or loss to follow up.</p> <p>Demographic and descriptive data will be compared for the two groups (olanzapine vs. placebo) using t-tests for continuous data and chi-square or Fisher's exact tests for categorical data where appropriate. Chi-square or Fisher's exact will also be used to analyze the primary endpoint of CR for group differences while logistic regression will be used to explore the additional effect of potential confounding variables. Chi-square or Fisher's exact tests will be used to analyze the secondary outcomes of rate of no significant nausea, CP rate, and incidence of discontinuation of study drug. A poisson or negative binomial analysis will be used to analyze number of emetic episodes and number of rescue medications used. All analyses will be performed using SAS© 9.4 at a Type 1 error rate of alpha=0.05.</p>	<input type="checkbox"/> N/A
<p>b. <i>When applicable, provide a power analysis:</i> Based on discussion with our biostatistician, using 80% power and an alpha of 0.05 the sample size is 49 patients per group to detect a 25% difference between groups (65% triplet therapy alone vs. 90% added olanzapine). We will recruit 98 patients. Therefore, we estimate patient accrual for 2 years.</p>	<input type="checkbox"/> N/A
<p>c. <i>Describe how data and specimens will be handled:</i></p>	<input type="checkbox"/> N/A
<p>i. <i>What information will be included in that data or associated with the specimens?</i></p> <p>Demographics: age, gender, race, weight, history of alcohol abuse, cancer diagnosis, and chemotherapy regimen. For efficacy analysis: number of emetic episodes, number of rescue antiemetic doses (dexamethasone, ondansetron, metoclopramide, prochlorperazine, promethazine, lorazepam, scopolamine, dronabinol), and patient scoring of nausea on VAS.</p> <p>For safety analysis, discontinuation of study drug due to adverse events or patient request.</p> <p>The aforementioned data will be collected by reviewing the patient charts and querying the electronic pharmacy software system. The number of emetic episodes is recorded during each nursing shift on the electronic medical record under the "Intake & Output" tab. The number of breakthrough antiemetics can be determined from the electronic pharmacy software system which tracks doses dispensed as well</p>	

	<p>as on the medication administration record within the electronic medical record as documented by the nursing staff. The VAS will be filled out by each subject and collected from investigators as described above.</p> <p>Data collection will be performed from the first day of chemotherapy through five days after the last dose of chemotherapy.</p>
ii.	<p><i>Where and how data and/or specimens will be stored?</i></p> <p>All data will be stored on the institutional secure R drive if in electronic format or locked in a secure file format if in paper format. Additionally, our pharmacy investigational drug staff will be responsible for storage of our study binder per their IDS policies. All randomization information will be kept in IDS storage.</p>
iii.	<p><i>How long will the data and/or specimens be stored?</i></p> <p>Data will be stored until the final project manuscript is complete and data storage is no longer required.</p>
iv.	<p><i>Who will have access to the data or specimens?</i></p> <p>Only the principal investigator (Julianne Orr) and co-investigators (Amber Clemmons, David DeRemer, and Stephen Clark) will have access to data collected. No specimens will be collected or analyzed during this study.</p>
v.	<p><i>Who is responsible for receipt or transmission of the data and/or specimens?</i></p> <p>N/A</p>
vi.	<p><i>How will data and/or specimens be transported?</i></p> <p>No data or specimens will be transported.</p>

8. Provisions to Monitor the Data to Ensure the Safety of Subjects

This study involves no more than minimal risk study and this section is not required. N/A

a.	<p><i>Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.</i></p> <p>A planned interim analysis will be completed when we reach 30 patients. This interim analysis will be un-blinded only for investigator Julianne Orr. The remaining study investigators will continue to be blinded for ongoing study purposes.</p>
b.	<p><i>Describe what data are reviewed, including safety data, untoward events, and efficacy data.</i></p> <p>Data for each study subject will be assessed and monitored daily during the study period. If at any point an untoward event occurs which study investigators, physician, or subject feels is related to the study the subject may be removed from the study. Ongoing safety analysis would occur for these subjects.</p>

<p><i>c. Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).</i></p> <p>Patients will be routinely followed in both the inpatient and outpatient settings. Subjects located on the inpatient setting will be assessed daily by study investigators and outpatient subjects will be assessed at the follow-up standard of care visit after chemotherapy.</p>
<p><i>d. Describe the frequency of data collection, including when safety data collection starts.</i></p> <p>Data will be collected daily for study subjects and will end five days after completion of chemotherapy.</p>
<p><i>e. Describe who will review the data.</i></p> <p>Study investigators will review all safety data.</p>
<p><i>f. Describe any conditions that trigger an immediate suspension of the research.</i></p> <p>If a request of greater than 10% of the goal patient population (110) is made for patients to drop out the study for any reason, the study will be discontinued at that time with analysis of the data.</p>

9. Withdrawal of Subjects

N/A

<p><i>a. If applicable, describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.</i></p> <p>Click here to enter text.</p>	<p><input checked="" type="checkbox"/> N/A</p>
<p><i>b. If applicable, describe any procedures for orderly termination.</i></p> <p>Click here to enter text.</p>	<p><input checked="" type="checkbox"/> N/A</p>
<p><i>c. If applicable, describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.</i></p> <p>If a subject chooses to withdraw from a study at any time, no further data will be collected. Safety data will continue to be assessed for the remainder of the study period. They will continue to receive standard medical care.</p>	<p><input type="checkbox"/> N/A</p>

10. Risks to Subjects

a. List the reasonably foreseeable risks.

As olanzapine (the study drug) is FDA approved medication and has been studied for this indication previously, the estimated risk to the patient is minimal. Olanzapine is currently approved for use in CINV per the NCCN guidelines. Any patient who has an allergic response to olanzapine will not receive further doses but will continue to be followed during the study period for outcome assessment (intention to treat analysis). The incidence of allergic reaction to olanzapine is rare (<1%) and not anticipated. Additionally, patients with a significant psychiatric history currently on other psychiatric medications will be excluded as per prior olanzapine study designs.

Olanzapine's side effect profile consists of central nervous system effects such as drowsiness, dizziness, and insomnia. Additionally, with long term use olanzapine has been associated with weight gain and hyperglycemia. Patients in this study will be taking olanzapine on days of chemotherapy and for 3 days post chemotherapy, which puts them at minimal risk for side effects that are associated with long term use. A phase I trial was conducted adding olanzapine to granisetron plus dexamethasone prophylaxis to determine the optimal dose of olanzapine for CINV prophylaxis for patients receiving their first cycle of HEC (cyclophosphamide, doxorubicin, platinum, irinotecan). The dose limiting toxicity was found to be depressed level of consciousness. The maximum tolerated dose was determined to be 5 mg on the two days prior to chemotherapy and 10 mg on the days of and the seven days after chemotherapy⁶. Therefore, the risk of olanzapine in the setting of this study is considered minimal and potential benefits outweigh these risks.

b. If applicable, describe any costs that subjects may be responsible for because of participation in the research.

Subjects will not be responsible for any cost due to participation in this study. The University of Georgia College of Pharmacy is funding the acquisition of the olanzapine tablets and the placebo tablets (similar size and color).

N/A

c. If applicable, describe risks to others who are not subjects.

Click here to enter text.

N/A

11. Potential Benefits to Subjects

Describe the potential benefits that individual subjects may experience from taking part in the research.

One of the most discussed problems among cancer patients is nausea and vomiting. These symptoms often lead to a decreased quality of life, malnutrition, and dehydration. Patients who participate in this trial may benefit from less chemotherapy induced nausea and vomiting, resulting in a more pleasant treatment experience. The patients who are not randomized to the olanzapine treatment arm will still receive standard of care medications (fosaprepitant, ondansetron, dexamethasone) and therefore will not be at risk for any additional untoward adverse outcomes.

12. Confidentiality

Describe the procedures for maintenance of confidentiality.

Only study personnel will collect and handle data consisting of patient specific information. All electronic data will be stored in the R drive. All randomization documentation will be stored with the IDS pharmacy staff per their policies and procedures. Lastly, VAS documents will be de-identified to only contain an ID number which correlates to a study subject. These forms will be collected and kept in a locked office by study personnel.

13. Consent Process

If you are obtaining consent of subjects describe the consenting process.

Once a patient is identified as a potential study subject with the approval of the primary team, one of our study staff will approach them regarding consent in person. Patients will be given the consent form, which will be reviewed with them by study personnel. The patient will be able to read and review the process prior to making a decision to be included in this trial. If a patient declines to consent, no further action is taken. If the patient signs the consent, the form will be stored in a binder in a locked office.

14. Compensation for Research-Related Injury

This section is not required when research involves no more than Minimal Risk to subjects. **N/A**

a. *Describe the available compensation in the event of research related injury.*

Click here to enter text.

15. Resources Available

N/A

a. *Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.*

Due to the study design, no psychiatric issues are anticipated, but a psychiatry consult is available per routine medical care if necessary. Additionally, medical services are available per standard care of practice, and patients will be closely monitored in both the inpatient and outpatient settings. Standard practice dictates close monitoring of these patients regardless of study participation.

- b. Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

Each member of the study team will be educated by the primary investigator, Julianne Orr, on their role and protocol procedures. Prior to initiating the study everyone will be competent in their duties and functions. IDS staff is competent in their ability to randomize study subjects and complete appropriate packaging and documentation, as per pharmacy procedures. They will ensure that anyone who will handle study procedures is properly trained. Additionally, the primary investigator will give an inservice prior to initiation of this study to all faculty and staff in both the hematology/oncology inpatient and outpatient settings (attendings, fellows, nursing, and pharmacy staff) to ensure everyone is aware of the aims and methods of this study.